EVENT RELATED POTENTIAL MONITORING AND ANALYSIS IN HEALTH AND DISEASE

A THESIS

submitted for the award of the degree

of

DOCTOR OF PHILOSOPHY

by

A. G. RAMAKRISHNAN

BIOMEDICAL ENGINEERING DIVISION

DEPARTMENT OF APPLIED MECHANICS

INDIAN INSTITUTE OF TECHNOLOGY, MADRAS

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CERTIFICATE

This is to certify that the dissertation entitled "EVENT RELATED POTENTIALS AND ANALYSIS IN HEALTH AND DISEASE" submitted by Mr. A.G.RAMAKRISHNAN to the Indian Institute of Technology, Madras, for the award of the degree of Doctor of Philosophy in Biomedical Engineering is a bonafide record of research work carried out by him under my supervision and guidance. He fulfills the requirements of the regulations laid down for the degree. The contents of this thesis have not been submitted to any other University or Institute for the award of any degree or diploma.

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A.G.RAMAKRISHNAN

Dedicated to

my beloved mother

Radha

and

loving father

Ganesan

ABSTRACT

This dissertation presents application of various (time domain, frequency domain and waveshape) analysis techniques on the evoked potentials(EPs) and compound nerve action potentials (CNAPs) obtained from a number of subjects. An IBM PC/XT compatible has been converted into an evoked potential averaging system by the addition of a dedicated circuit card and an external two channel instrumentation amplifier, whose gain and passband are both programmed from the personal computer keyboard.

Using this system, central and peripheral neural responses were obtained from 25 normals and 21 leprosy patients following electrical stimulation of the median nerve at the wrist. Parameters such as motor threshold of stimulation, amplitudes and relative latencies of the dominant peaks, segmental nerve conduction velocities(NCV) and the central conduction times(CCT) were obtained from the various waveforms. The amplitudes of the digit and elbow CNAPs are found to be much higher in the case of normals with no overlap between the range of values for normals and patients with clinically confirmed median nerve involvement. In the spectral domain, the patient data exhibit peaks at specific frequencies, the origins of which are not yet known. A multivariate analysis technique was applied to the time domain data and the results show that only the two peripheral response amplitudes, the two distal segmental NCVs and the stimulus threshold to evoke a minimal thumb twitch are the principal factors in discriminating between normal and abnormal subjects. The fall times of the main peaks of all the responses, the CCT and the amplitudes of the brachial plexus and the cortical EPs

are not significantly different between normals and patients and thus cannot help in the classification of a new data as belonging to one or the other group.

Finally, a waveform classification technique based on a skeletal tree representation of the responses was applied on the data. The patient data trees were matched to a reference normal data tree by means of a number of node splitting and node merging operations and the distance between the two waveforms was defined as the number of tree operations required to match the two trees. It is found that the scheme is effective in classifying the data.

The results indicate clearly that the CNAPs recorded from the median nerve in the forearm and third digit show discernible abnormalities much earlier to the clinical manifestation in the form of sensory or motor deficit. In fact, in a field situation, for a preliminary screening of the exposed population, it suffices to take only the digital response to median nerve stimulation at the wrist and to note the motor threshold of stimulation. A quick decision can be taken and the whole testing procedure will take only 15 minutes. A portable field unit has also been designed for this purpose. That the leprosy bacilli do not infect the central nervous system is confirmed by the normal features of the cortical potentials. The reduction in the amplitudes of all the peripheral potentials implies a considerable reduction in the number of active, fast-conducting sensory nerve fibres.

In summary, the applicability of electrophysiological tests in early detection of leprosy is quantitatively established.

CONTENTS

1. INTRODUCTION

1.1 CLINICAL NEUROPHYSIOLOGY

Electroencephalography(EEG) and electromyography(EMG) arose from experiments in the physiology laboratory where Lord Adrian and his colleagues exploited the then new electronic techniques, such as vacuum tube amplifiers, for the study of electrical activity from brain and muscles of humans and other animals [Adrian and Bronk, 1929]. Starting nearly 50 years ago, first EEG, then EMG laboratories evolved in hospitals for the physiological investigation of patients. Advances in technology and neurosciences have facilitated rapid growth in this field, which now requires full time physiological, medical and technical specialists. Although similar techniques and scientific understanding are employed, EEG and EMG developed within different specialities, since they study patients with different types of disorders. With the advent of microprocessors, minicomputers and other means for recording evoked potentials, boundaries between EEG and EMG techniques have disappeared and they are now combined under the term 'Clinical Neurophysiology'.

The above mentioned investigations have proved useful for detection, registration and quantification of various disturbances of functions in the central or peripheral nervous systems and neuromuscular apparatus. They are the electrophysiological counterparts to morphological techniques provided in neuropathology laboratories by biopsy and radiology departments, including CT scans. In this important respect,

clinical neurophysiology forms one of the bases of 'quantitative neurology', providing the clinician with objective information to aid his clinical assessment.

1.2 EVOKED POTENTIALS

One of the most useful techniques in clinical neurophysiology is the recording of evoked potentials (EP). An EP is an electrical manifestation of the neural response (central or peripheral) to an external sensory stimulus. The stimulus could be flashes of light, auditory clicks presented through an earphone, current or voltage pulses delivered to a peripheral nerve, or an alternating, black-and-white, checkerboard pattern presented on a TV screen. Also called Event Related Potential (ERP), an EP is usually picked up on the intact scalp along with the ongoing EEG. Further, in the case of electrical stimulation of peripheral sensory nerves, additional recording electrodes may be placed at peripheral sites along the course of the nerve fibres.

The study of evoked potentials in the human central nervous system (CNS) began in 1947 with Dawson's use of photographic superimposition of the poststimulus EEG to demonstrate a waveform following peripheral nerve stimulation [Dawson, 1947]. He observed that a patient with myoclonic epilepsy had a somatosensory evoked potential (SEP) of much higher amplitude than normal. As amplifiers have improved and computers have become more easily obtainable to carry out signal averaging, many laboratories are studying evoked potentials, especially the low

amplitude, short latency ones which are of particular clinical interest.

Most EPs cannot be seen in routine EEG recordings because of their admixture with background brain wave activity and artifacts. The ERP, whose amplitude is in the range of 0.1 to a few microvolts, is obscured by the EEG, whose amplitude is usually of the order of tens of microvolts. Therefore, the evoked potentials must be extracted by the technique of computer signal averaging. Being time-locked to the stimulus, an EP always appears at the same interval after the stimulus, whereas the other electrical activity, namely, EEG is not stimulus-coupled. Hence, the desired EP is detected by digitally averaging the signals recorded after repeated stimuli. The EEG and artifacts, which are statistically random in nature, are thereby diminished and the time-locked EP is summed and clarified, as the stimulus is repeated many times. It can be shown that averaging improves the signal to noise ratio by a factor of $\sqrt{N}$, where N is the number of averages. EPs provide accurate, objective and completely reproducible data about sensory systems [Chiappa and Ropper, 1982] and are very sensitive to dysfunction in sensory pathways and can detect abnormalities even before they are evident through physical examination. Evoked potential studies could be considered as an extension of the physical examination, thus revealing covert and overt disorders in pathways tested. One or more electrical potentials(waves) may appear after a stimulus; since each is generated by a specific anatomic structure, sensitive physiologic evaluation of sensory structures and their

interconnections is possible. The presence or absence of appropriate EP waves and their latencies(the elapsed time from stimulus to wave peak or the time between peaks) are the major features hitherto used in clinical interpretation.

Three EP tests have been standardized : Pattern - reversal visual(VEP), brainstem auditory(BAEP) and short-latency somatosensory(SSEP) evoked potentials. They have the ability to reveal the presence of clinically unsuspected lesions, particularly in the diagnosis of multiple sclerosis ; to help define the anatomic distribution of a disease process ; and to monitor continually, during surgery, the integrity of the neural pathways in the spinal cord, which cannot otherwise be examined clinically, when the patient is under anaesthesia [Brown and Nash, 1979]. An abnormal EP has a high probability of indicating a nervous system lesion. Only the SSEPs are relevant for the present work and hence the auditory and visual EPs will not be discussed here.

1.3 COMPOUND NERVE ACTION POTENTIALS

A volley of impulses evoked by electrical stimulation of a nerve can be recorded along the course of the nerve, especially when it lies close to the skin. These potentials, termed as Compound Nerve Action Potentials(CNAP), are used clinically to measure peripheral nerve conduction velocities [Brown, 1984] and, were initially not considered as part of EP studies. However, peripheral nerve conduction should, as a routine, be studied simultaneously with the central evoked potentials. This is

because (a) it confirms that an adequate stimulus has been delivered to the nerve being examined, (b) it establishes the normality or otherwise of conduction along the peripheral segment of the nerve, and (c) it reveals information regarding conduction across spinal roots into the spinal cord and any pathology arising therefrom [Private communication, Dr. S.S.K. Ayyar]. Also, it is very helpful to record potentials close to the spinal cord (at Erb's point in the case of upper limb stimulation, or over the sciatic notch in the case of lower limb stimulation). In such cases, the peripheral latencies, upto the point of entry of the nerve into spinal cord, can be used as a time mark, from which interwave latencies are measured, with a view to determine the central conduction time. Latency variability of subsequent waves due to differing limb lengths and conduction velocities can be minimized through such measurements of interwave latencies.

Lesions of peripheral portions of the sensory pathways, including the receptor end organ, can produce clinical signs that are consistent with central lesions as well. EP recording, together with peripheral conduction study, following distal stimulation of the nerve, is often an effective method for differentiating between such peripheral and central disorders. Sequential recordings of potentials, at multiple sites along the course of peripheral nerves, at various spinal levels, and from the scalp, can be used to precisely define the level of a lesion. This method is particularly valuable since it provides a direct, non-invasive means for localizing lesions of the brachial plexus and dorsal roots. The interwave latencies evaluated therefrom

form the vital basis for clinical interpretation, in addition to morphological and amplitude characteristics of the recorded waveforms.

1.4 NEURAL INVOLVEMENT IN LEPROSY

The study of EPs and CNAPs thus significantly help in the diagnosis and assessment of various neuropathies. Leprosy is a disease principally affecting the peripheral nerves and this thesis deals with the application of the above mentioned electrophysiological techniques to leprosy. Hansen's disease continues to be a serious challenge in most developing countries, contributing significantly to the physical and social disability of the patients afflicted. Because of the strong stigma associated with it, leprosy is still one of the most trying diseases that man has to endure. However, an effective cure is possible if the disease is identified early and treatment commenced quickly. It is estimated that approximately 25% of the patients who are not treated at an early stage of the disease develop anaesthetic conditions of the extremities and/or deformities of the hands and feet. As a single disease entity, leprosy is one of the foremost causes of deformities and crippling.

Hanseniasis is a chronic infectious mycobacterial disease primarily affecting the peripheral nervous system and secondarily involving skin and certain other tissues [Jopling, 1984]. There is some involvement of peripheral nerves in all patients with leprosy, but it is not always clinically detectable. The nerves

may be involved at any level from the peripheral cutaneous nerve twigs to the dorsal root ganglia. Mycobacterium leprae is thought not to affect the spinal cord or the brain [Thangaraj and Yawalkar, 1986], though there has not been any electrophysiological basis for this till now. The basis of the lesion in peripheral nerves is the bacillus' neurotropism [Charosky et al., 1983].

The neurological involvement in leprosy may be summarized as follows : The Schwann cells around the peripheral nerve fibres are the main sites of multiplication of leprosy bacilli. There is centripetal, centrifugal as well as ramificatory (from one lateral nerve bundle to another) spread of infection. The natural consequences of this infection are segmental demyelination and axonal degeneration [Srinivas and Ramanujam, 1981].

Thus the main emphasis in leprosy control must be in early diagnosis, quantification of neural involvement and early, adequate drug treatment.

1.5 EARLIER STUDIES IN LEPROSY

Slowing of conduction and conduction block have been observed in other primary demyelinating neuropathies like diphtheritic polyneuropathy, Guillain-Barre polyneuropathy and metachromatic leukodystrophy [Shahani and Sumner, 1981 ; Brown, 1984]. Dash [1968] reported that sensory potentials were recorded in leprosy patients from the afferent nerves supplying anaesthetic areas, and therefore, a loss of sensation in leprosy did not necessarily mean destruction of all nerve fibres. He

reported a reduction in conduction velocity of ulnar nerves in all forms of leprosy and suggested that a prolongation of the refractory period of the nerve fibres probably preceded the reduction in velocity. Gourie-Devi[1984], in a study of twelve Hansen's disease patients, observed a decrease in amplitude of the sensory potentials of the greater auricular nerve in more than 50% of the patients, whereas the increase in latency was observed only in a few cases. In about 50% of the cases, a significant difference in latency and amplitude between the right and left nerves was also reported. Kyriakidis et al. [1983], studied the integrity of the autonomic control of the cardiovascular system in 21 lepromatous leprosy patients using simple tests based on cardiovascular reflexes. They reported impairment of both parasympathetic and sympathetic functions. Schochina et al. [1983], reported that out of the 17 leprosy patients whose Hoffman reflex in the tibial nerve was examined, 12 had a pathological response. Chun and Shi [1984], based on pathological studies on biopsy material of peripheral nerve tissue from 210 patients, reported that lesions were most common in the ulnar (85.7% in the Polar Tuberculoid[TT] type, 98.3% in Lepromatous Leprosy [LL] type), peroneal(77.8% in TT, 97.9% in LL), median(80% in TT, 90.2% in LL), radial(66.6% in TT, 82% in LL), and the great auricular, tibial and supraorbital nerves. The ratio of bilateral nerve involvement in the same nerve was higher than unilateral involvement (approximately 5:1).

Antia et al.[1970] carried out clinical, electrodiagnostic, surgical and gross morphologic investigation of peripheral nerves

in 22 patients of polyneuritic leprosy. They reported abnormalities in the ulnar innervated muscles suggestive of denervation and reduced motor conduction velocities in ulnar and median nerves in the forearm, the reduction in the former being more common and pronounced. Mary Verghese et al.[1970], in a study of 96 leprosy patients, found a marked slowing of the motor conduction velocity in the upper arm segment of the ulnar nerve in patients with clinical evidence of neural involvement. Sohi et al.[1971] observed that there was an overall reduction in the motor conduction velocity in all the nerves of the patients that they tested (ulnar, median, posterior tibial and common peroneal). Sebille and Gray [1979] recorded electromyograms from left peroneus longus and left tibialis anterior muscles innervated by the popliteal nerve in 13 lepromatous leprosy patients; reduction of motor unit potentials during maximal voluntary contraction was observed in two thirds of the muscles examined.

1.6 SCOPE OF THE PRESENT STUDY

Since the sensory nerves are the first to be affected, it is only natural to search for early lesions through an assesment of sensory functions. However, for reasons not clear, very little work has been done to study peripheral and central nerve lesions in leprosy. Although studies of sensory conduction [Mc Leod et al., 1975 ; Hackett et al., 1968] and motor conduction [Swift et al., 1973] have been reported in the literature, to this day, to the knowledge of the author, no cerebral evoked potential studies

on leprosy patients have been reported.

The work reported here involved study, comparison and classification of peripheral and central event related potentials obtained by stimulation of the median nerve of normals and leprosy patients. The purpose of the study was to examine both peripheral and central nerve conduction and to obtain amplitudes, velocities and waveshapes of compound nerve action potentials at palm, forearm and arm as well as to obtain the central conduction time from brachial plexus (Erb's point) to the contralateral somatosensory cortex. An IBM-PC/XT compatible microcomputer has been converted into a versatile evoked potential averaging system by adding suitable hardware and software. The dedicated hardware designed and developed here has given the system capabilities of acquiring compound nerve action potentials and event related potentials following electrical stimulation of peripheral nerves. This general purpose computer (IBM-PC/XT compatible) facilitated the storing of the averaged data in floppy disks, computing of the power spectra of the data and other computations, such as, classification of normal and patient waveforms. A completely programmable, two-channel, instrumentation amplifier has been designed and used to pick up the biopotentials.

Employing the above system, nerve conduction data and short-latency somatosensory evoked potential data have been obtained from 25 normals and 21 leprosy patients after stimulation of their median nerves at the wrist. The neurophysiological data so collected have been analyzed both in the time and frequency domains. The amplitudes and durations of the neural responses

were measured from the acquired waveforms and the nerve conduction velocities have been computed. These data, together with the stimulus thresholds, have been studied in relation to the clinical data of the patients, such as loss of sensibility and/or motor power. The central conduction times of both normals and patients were obtained and compared. Discriminant analysis was applied to evaluate the effectiveness of the various time domain parameters in distinguishing the abnormal from the normal nerve action potentials and the key parameters have been identified. The power spectra of potentials from patients have been studied in comparison with those of normals. Also, a scheme has been devised to classify the normal and patient responses. In this, the waveforms have been represented by means of a skeletal tree structure and an algorithm for tree matching has been applied to classify the data.

The work has been explained in detail in the chapters that follow. The experimental data unambiguously confirms that the central nervous system is spared in leprosy. The results indicate clearly the viability of using peripheral nervous system monitoring as an important method of early detection of leprosy. It is thought by incorporating these methods for clinical evaluation of the suspected population, it is possible to diagnose the disease earlier than hitherto possible, leading to better management and ultimate control of the disease.

2. INSTRUMENTATION

2.1 INTRODUCTION

Evoked Potential(EP) systems are not manufactured in India and the cost of imported systems is exorbitantly high. Further, most of the commercially available EP averagers do not support further processing (like spectral analysis) of the acquired compound nerve action potentials(CNAPs) and evoked potentials. Hence there is a need to have a custom-designed system with the above capabilities. The hardware and software requirements for such a system are : (i) an isolated electrical stimulator with adjustable intensity, (ii) a two channel, low noise, high input impedance, electrically isolated instrumentation amplifier, (iii) a sufficiently fast digitizer with good accuracy, (iv) a digital averager to add acquired data sequentially, (v) a monitor to display the averaged waveform, (vi) necessary software to select the various parameters of stimulation and acquisition and to enable measurements from the monitor, and, (vii) a software package for further processing of EP data.

Accordingly, an evoked potential averaging system has been built around an IBM-PC/XT compatible microcomputer. Fig.2.1 illustrates the block diagram of the neuroaverager. As is clear from the block schematic, the system has capabilities to acquire auditory and visual evoked potentials and electromyogram besides somatosensory evoked potentials. Since only the somatosensory EPs are relevant for the present work, details of visual and auditory stimulators are not discussed here.

A dedicated circuit card was designed to fit into one of the standard expansion slots of the PC. This card contains a two channel 12-bit analog to digital converter (ADC) and necessary circuits to provide isolated electrical stimulation to any peripheral nerve or muscle. The stimulus is a rectangular voltage pulse whose width, intensity and repetition rate are programmable over a wide range. Outside this system is a two channel, low noise and high gain amplifier. The passband and the gain of the amplifier are software programmable and there is also a digitally controlled automatic gain control which can be enabled or disabled by the software. The electrode to skin contact impedance can be checked against a pre-fixed value.

The dedicated user-friendly software package developed enables easy channel selection, electrode impedance check and control of all the above mentioned programmable parameters. The number of stimuli to be presented and the signal acquisition time (sweep) after each stimulus delivery are also easily programmed. A vertical cursor on the screen enables measurement of absolute latency (elapsed time from stimulus to occurrence of response), relative latency (time between different response peaks) and amplitude and also aids in the computation of nerve conduction velocity. There is provision to superimpose on the screen two or more averaged responses for visual evaluation of the waveforms.

2.2 FABRICATION OF ELECTRODES

The various stimulating and recording electrodes as well as the head strap for securing the scalp electrodes in place, used

for the work reported in this thesis, were conceived and fabricated by the author in the laboratory.

The stimulating electrodes as also the pick-up electrodes at the digit and the elbow are dual silver discs, 8 mm in diameter and 25 mm apart, embedded in a rectangular perspex holder. The metal discs are in shallow cavities which are meant to hold a small amount of conductive electrode paste. Another pair of stimulating electrodes was obtained by suitably modifying a 2-pin standard electrical plug. Appropriate connectors which fit into the electrical stimulator output socket of the system, have been connected to the other end of the plug cable. This electrode is very useful in exploring and locating the optimal stimulus site where the nerve stimulation is achieved with minimum stimulus voltage. For the Erb's point recording site, a single silver disc was fastened to a rectangular perspex base of such dimensions that it sits conveniently in the supraclavicular fossa. A commercial Z-type electrode has been used as the scalp electrode. A leather strap was made, to be worn on the head. The strap is attached to the head by means of velcro strap over the jaw, similar to securing a helmet. The strap has several rubber bands which can be tightened to strongly hold the scalp electrodes in position. The ground electrode is a silver disc, 2 cm in diameter, attached with araldite to a perspex top. The latter has a protuberance which facilitates securing of the electrode onto the electrode site with velcro.

2.3 DESIGN OF THE AMPLIFIER

The Fig.2.2 presents the circuit diagram of the amplifier. Due to patent requirements, the complete details of the various circuits are not provided. The two input channels are identical. Each channel has a single integrated circuit, instrumentation amplifier (IC1 and IC2) at the input stage which has a common mode rejection ratio of 110dB, an input impedance of 3×10^9 ohms in parallel with 3pF and very low noise(1.3μV RMS referred to the input, 0.1 Hz to 10 KHz). This stage has a gain of 100, followed by another amplifier, also of gain 100. The latter is followed by a high pass(low-cut) filter with software selectable cut-off frequencies of 1,10,90 and 100 Hz. The selection is achieved by switching in suitable resistances by means of analog gates (IC4 and IC8). The analog switches are, in turn, controlled by the outputs of serial to parallel converters(IC6 and IC7), which get serial data as input from the computer. The high pass filter is followed by a low pass filter with programmable high-cut frequencies of 150, 200, 1000 and 3000 Hz. Once again, analog switches are employed to obtain this selection. The next stage is a programmable gain amplifier, with amplification values selectable between 1, 10, 100 and 110. Analog switches (IC5 and IC9) aid in the gain selection by switching in appropriate resistors. The final amplifier has programmable gains of 1, 2, 3 and 4 and its output is fed to a buffer. A shielded cable connects the amplifier to the circuit card in the microcomputer.

The user selects the mode required, namely, Nerve Conduction or Evoked Potential. Depending upon the mode selected, the system

chooses the default cutoff frequencies, which can be interactively changed by the user, if and when necessary. The appropriate control byte is then determined and sent serially from the computer to the amplifier. To begin with, the amplifier is programmed to have minimum gain and the output of the amplifier is tested for its amplitude after digitization. If the amplitude is much below the input range of the analog to digital converter, the gain is automatically increased by one step. The amplitude is again checked and the gain adjusted, and so on, until the amplifier output is marginally lower than the input range of the ADC. This scheme makes the best use of the dynamic range provided by the 12 bit ADC.

The impedance check facility is made possible by the use of a comparator and analog switches. One electrode at a time is introduced as one of the impedances of a voltage divider whose other impedance is a fixed reference resistance. The output of the voltage divider is compared with a reference voltage. Thus, the output of the comparator indicates whether the electrode-skin interface impedance is above or below the allowable maximum value. The comparator output status is read by the system through an input port.

2.4 DATA ACQUISITION

The data acquisition,timing and control circuitry is shown in Fig.2.3. This consists of a two channel digitizer, address decoding circuits to provide chip select signals to the various peripherals, a timer to control the sampling and the stimulus

repetition frequencies and an output port to program the amplifier, besides an input port to obtain the electrode, amplifier and timer status. The digitizer makes use of a twelve bit analog to digital converter which has tristate outputs connected directly to the personal computer data bus. The 12 bit data is read in as two bytes, first byte containing the leading eight bits, and the second byte comprising of the least significant four bits with 4 trailing zeros added. The conversion time of the ADC is 25 microseconds.

The outputs from the two channels of the instrumentation amplifier are sampled and held by separate sample & hold buffers. One channel at a time is selected by a high speed analog multiplexer controlled by the output port and the signal is fed into the analog input pin of the ADC. The start of conversion is timed by a 16 bit programmable binary counter whose input clock is derived from the microcomputer system clock. This counter sets a flip-flop whose output status is read by the system through the input port. As soon as the flip-flop output goes high, the conversion is started by outputting appropriate control signals.

2.5 ELECTRIC STIMULATOR

The circuit details of the somatosensory stimulator are given in Fig.2.4. An astable multivibrator (IC 23) generates pulses of duration 25 μsec and repetition frequency 300 Hz. These pulses are fed into a comparator whose output reference level can be changed using the output of a digital to analog converter (DAC). Thus, negative pulses of varying amplitude are produced

which drive the input of a pulse transformer through a two-transistor current amplifier. The ferrite core pulse transformer has a turns ratio of 1:80 and the stepped up output voltage is rectified and filtered to get a variable, high d.c. voltage. To deliver a stimulus, a pulse of width equal to the required stimulus duration is produced by suitably programming an output port. This pulse drives the input of an optocoupler whose output stage is used to deliver an electrically isolated stimulus pulse of amplitude equal to the rectified high voltage. This constant voltage pulse is presented through a Darlington pair. The entire stimulator can be disabled by raising the output reference voltage of the comparator to be the same as that of the supply voltage; the input of the pulse transformer has no excitation and hence the stimulator is disabled. The remnant rectified d.c. voltage, if any, is cleared by a bleeder resistor.

The stimulus repetition frequency is derived using another 16 bit programmable timer. Again the counter input clock is a submultiple of the computer system clock obtained employing another fixed binary counter. The stimulus recurrence rate is assumed by default or chosen by the user. The stimulus repetition period is then computed and the appropriate count value is calculated by the system and loaded into the counter. The stimulus intensity can be varied from a value of 20 volts to 250 volts. The possible values of stimulus duration are from 0.1 msec to 1 msec, in steps of 0.1 msec. The pulse repetition rate can be fixed from 5 Hz down to any fraction of a Hz.

2.6 SOFTWARE DETAILS

The software package written in Turbo Pascal incorporating 8088 assembly language routines wherever speed is critical (like data acquisition, etc.), exploits the dedicated hardware efficiently and thoroughly to acquire the various nerve conduction and evoked potentials and subsequently to measure the amplitudes and latencies from the obtained waveforms and then compute the conduction velocities. The software is menu driven and when the system is switched on, the main menu appears on the screen displaying the various modes possible, namely SEP (Somatosensory Evoked Potential), SNCV (Sensory Nerve Conduction Velocity), MNCV (Motor Nerve Conduction Velocity) and EMG (Electromyography). All selections are made through cursor movement keys. When one of the modes is selected, the corresponding next level menu shows the default values for that mode of all the parameters, viz. stimulus repetition rate, number of stimuli, stimulus intensity, low-cut and high-cut frequencies. The value of any parameter can be altered, if required, by selecting from a choice of values displayed by the sub-menu for that parameter. If all the default parameter values are acceptable, or when the necessary selections have been done, the averaging can be started by pressing a key.

When the averaging starts, the input data is checked after each stimulus for the presence of excessive artifact. Based on the maximum level of the input signal before stimulus delivery, a particular limiting value for the amplitude of the input samples is fixed. If more than 12.5% of the samples in a particular sweep

exceed this set limit, then that sweep is rejected and the reject count is incremented ; otherwise the data samples are added to the cumulative sums of corresponding samples of previous sweeps and the stimulus count is incremented.

After the required number of artifact-free sweeps are collected, the data is averaged and the EP/CNAP is stored in a floppy disk and then the waveform is displayed on the screen. In order to see the features of the waveform in good detail, it is scaled such that it occupies the entire monitor screen. The time axis(x) as well as the amplitude axis(y) are divided into ten divisions and the x and y scales are displayed. A vertical line-cursor is also provided which can be moved along the x-direction using the arrow keys. At every position of the cursor, the latency(time) and amplitude of the evoked waveform are displayed on the monitor. The occurrence time and the amplitude values corresponding to any number of peaks or valleys can be marked by the stroke of a key for printing later. In the case of nerve conduction studies, the nerve conduction velocity(NCV) can be computed by entering in the computer, the length of the nerve segment under test. The NCV so determined is automatically printed along with the waveform. Similarly, there is provision to measure and print interpeak latencies and amplitudes. The displayed waveform can be smoothed using a three point moving average filter at the stroke of another key.

Programs have been developed to obtain the absolute and relative power spectra of the evoked data, to smooth out the

spectra, to display and also to print the same.

2.7 CONCLUSION

A versatile system for averaging evoked potential data is necessary to obtain clinically relevant data from patients. Since evoked potential averagers are not manufactured in India, and an imported system with the required facilities will be prohibitively costly, necessity arose to custom-build a system. Accordingly, an IBM-PC/XT based system has been designed, fabricated and tested extensively. Fig. 2.5 shows the photograph of the IBM-PC/XT compatible circuit card and Fig. 2.6 shows the photograph of the card in place inside the microcomputer. Having been used to acquire data from around 50 individuals consisting of both normals and patients under a clinical setting, the system has been found to be quite reliable. All the measurements taken and reported in this thesis have been obtained using this system. This system has been in use in a reputed neurological clinic in Madras for the past 3 months. Data collection on patients has been found reliable and easy. The character and quality of the records obtained have been found to be very good.

Thus the system developed possesses all the necessary facilities for somatosensory evoked potential data collection, nerve conduction studies and further analysis of the acquired data. In fact, the design and development of this system (including the visual and auditory stimulators) amounts to a good import substitution / foreign exchange saving work and the system has enormous potential for commercial exploitation.

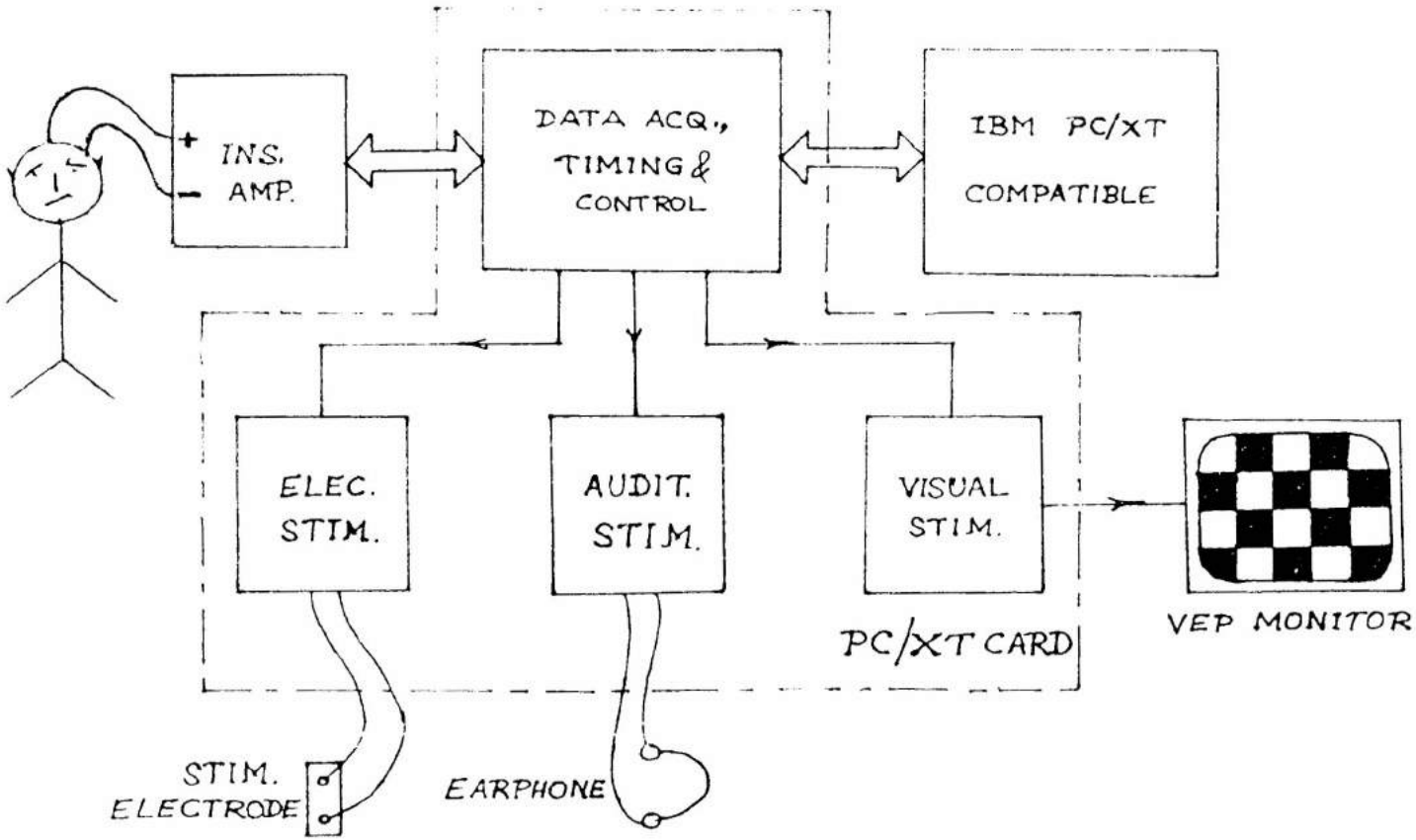


Fig. 2.1. BLOCK SCHEMATIC OF THE NEURO AVERAGER

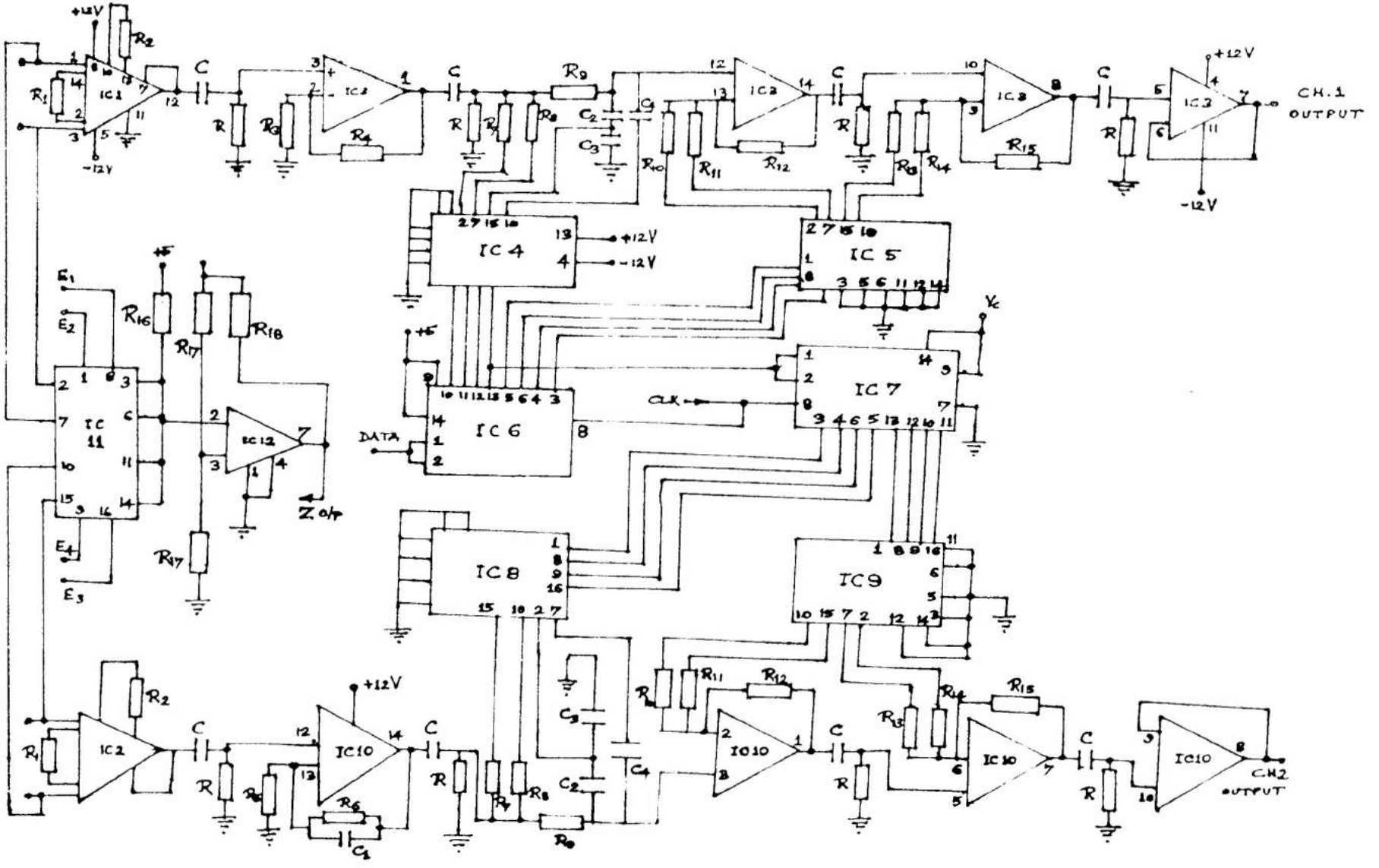


Fig. 2.2. INSTRUMENTATION AMPLIFIER

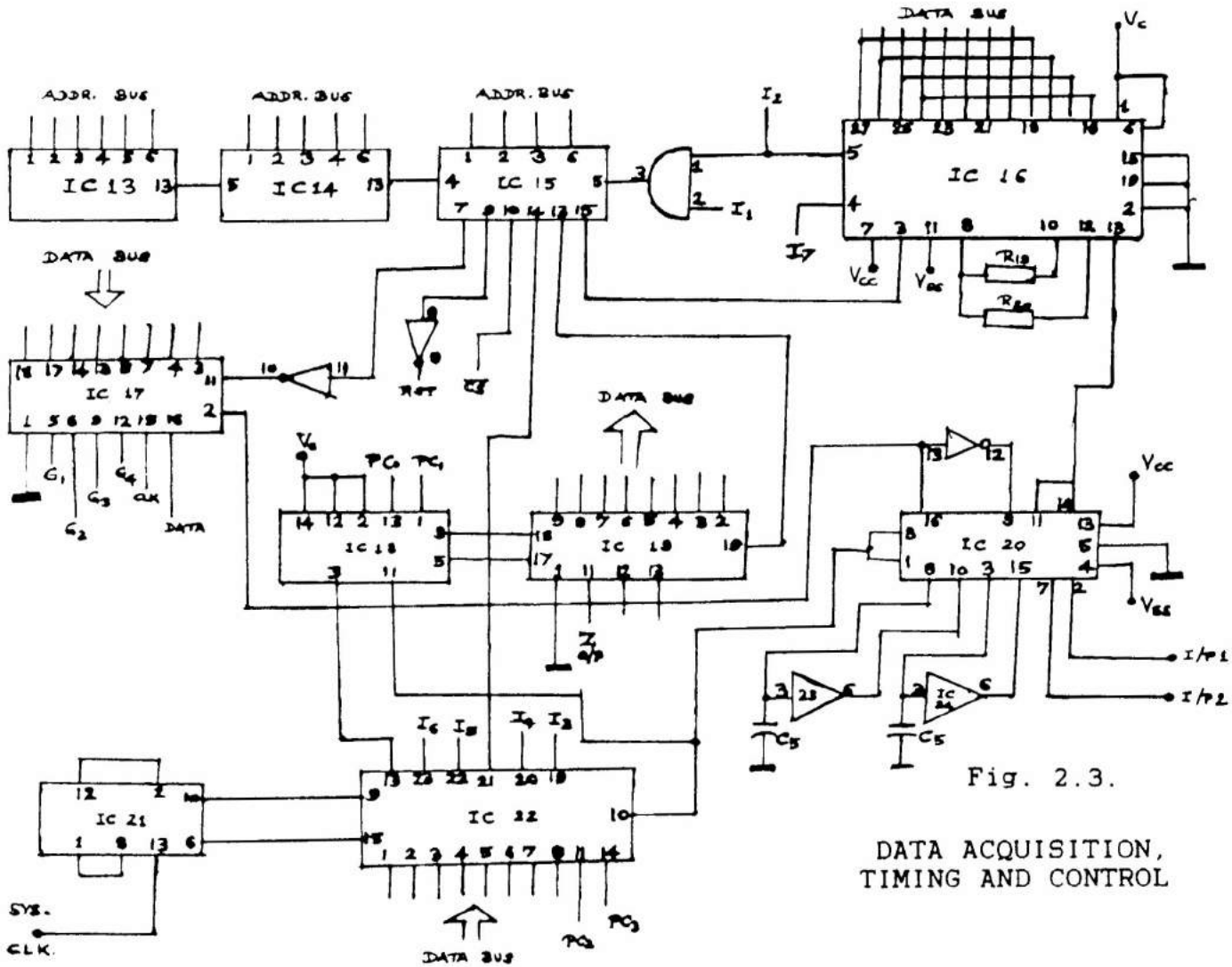


Fig. 2.3.

DATA ACQUISITION,
TIMING AND CONTROL

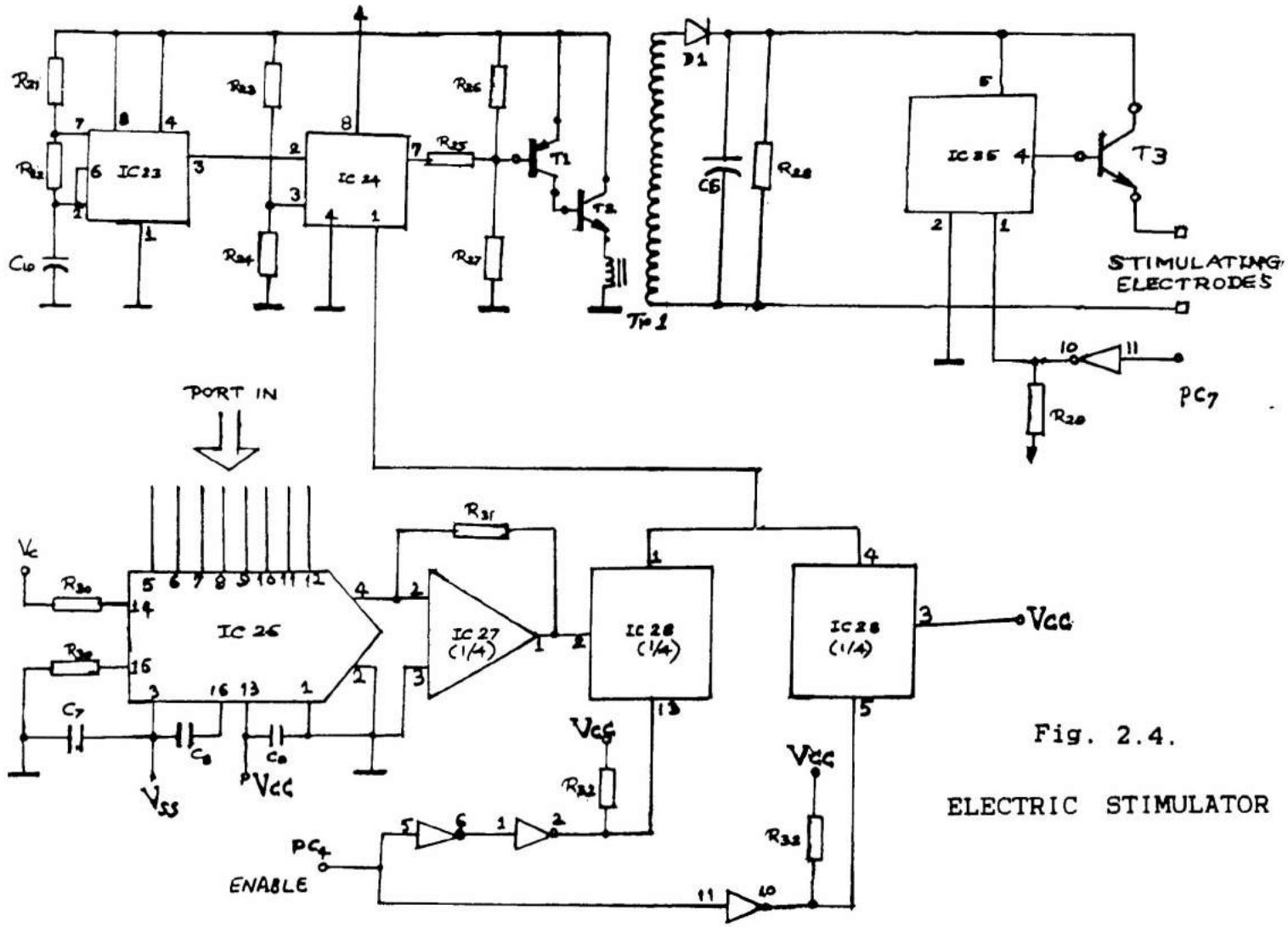


Fig. 2.4.

ELECTRIC STIMULATOR

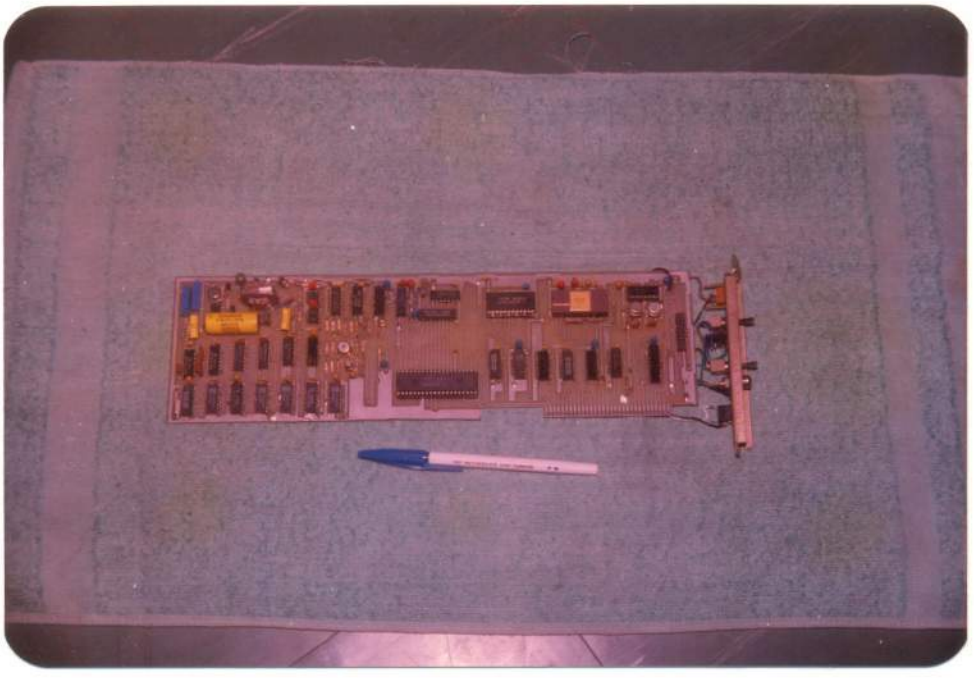


Fig.2.5. Photograph of the neuroaverager card

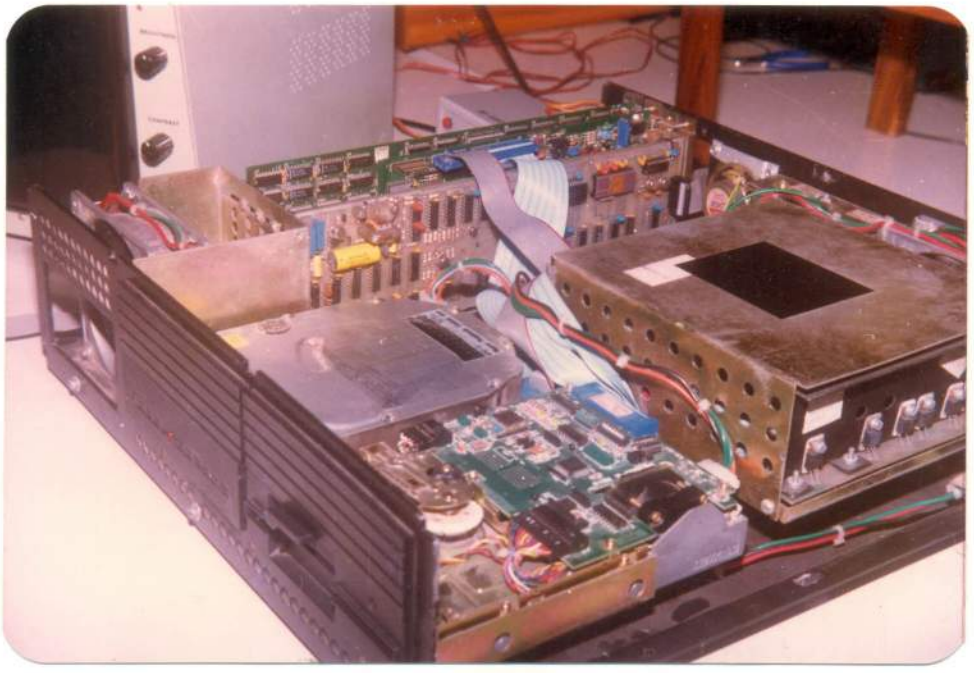


Fig.2.6. The card in place inside the computer

3. EVOKED POTENTIAL DATA COLLECTION

3.1 INTRODUCTION

Nerve conduction tests can detect changes in conduction velocity, response amplitudes and also reveal conduction block which arise due to focal or segmental demyelination. Thus, in leprosy, since the Schwann cell or myelin sheath around the nerve fibres is the main target of the bacilli, nerve conduction studies become extremely relevant.

The anatomical features of a myelinated nerve fibre which are important in determining its conduction velocity are : (i) diameter of the fibre, (ii) distance between the nodes of Ranvier and (iii) integrity of the myelin sheaths. In peripheral nerve diseases with segmental demyelination like Guillain-Barre polyneuropathy, striking abnormalities in the velocity of nerve impulse propagation are observed. According to Gilliatt [1966], reduction in the maximum conduction velocities by more than 40% from the mean normal value usually indicates the presence of segmented demyelination. By contrast, axonal polyneuropathies (associated with uremia, multiple myeloma, diabetes and malnutrition) result in reduction of sensory or motor response amplitudes or abnormalities of late responses rather than slowing of conduction velocities, especially if the pathological process tends to spare larger diameter axons [Shahani and Sumner, 1981].

Demyelination impairs the transmission of impulses primarily by changing the properties of the paranodal and internodal membranes. The loss of myelin increases the capacitance and

diminishes the transverse resistance in the paranodal and internodal regions. This entails increase in the outward leakage currents through these regions [Sumner et al., 1982]. The larger leakage currents increase the time the internal longitudinal current must flow in order to depolarize the next nodal membrane to threshold. This increases the internodal conduction time and slows down the transmission of the impulse. If the transverse current leakages are excessive, not enough current may be available to depolarize the nodal membrane to threshold and the impulse is blocked.

A study of the cortical evoked potentials along with the peripheral conduction potentials helps to locate the sites of neural damage and when the evoked potential latencies are reckoned from the peripheral conduction times upto the spinal cord, the central conduction time can be isolated. Thus abnormalities in central conduction per se can be identified. The possible changes in central conduction in leprosy have not been reported so far.

3.2 STIMULATION AND PICKUP LOCATIONS

The patient data for the present study were collected at the Central Leprosy Teaching and Research Institute, Chenglepet, South India. It is observed that in most of the Hansen's disease patients, ulnar nerve is the first to be affected. Because of fear, shame and social stigma associated with this disease, few people come to leprosy centres in the early stages. Thus, even in the outpatient department, almost all the patients reporting have

an advanced ulnar nerve involvement. This observation is in general agreement with the findings of earlier researchers. Antia et al.[1970], in a study of 22 leprosy patients, have reported that the ulnar innervated muscles of the hand and forearm were more frequently and more severely affected as determined by electromyography, than those supplied by the median nerve. They have also found more frequent abnormalities in motor conduction in the ulnar nerve than in the median nerve. Similar results of higher percentage and/or degree of involvement of ulnar nerves have been reported by Sohi et al.[1971], McLeod et al.[1975] and Mary Verghese et al.[1970] based upon motor nerve conduction velocity studies. The chief purpose of the work reported here has been to study the early changes in the affected nerves. So, ulnar nerve could not be considered, because, as explained above, it was difficult to get patients with minimal involvement of ulnar nerves. Thus, median nerve was selected for study in the patients. Most of the patients chosen had little or no clinical involvement of the median nerve in at least one side. This was done with an idea to find out the changes occurring early during the infection of median nerve and to extend the observations to ulnar nerve during the early onset of the disease.

The median nerve at the wrist, between the tendons flexor carpi radialis and palmaris longus, at the distal crease, was chosen as the stimulus site. Fig.3.1 illustrates the locations of the various stimulating and recording electrodes. Three peripheral locations and one scalp site were selected for pick-up. The peripheral sites of recording were: (i) the palmar side

of third digit (ii) just proximal to the elbow crease, medial to the brachial artery and (iii) the supraclavicular fossa over the brachial plexus at Erb's point. The central pick-up location is a point in the contralateral somatosensory cortical hand area, 7 cm towards the tragus of the ear from a point 2.5 cm posterior to the vertex[Jones, 1982]. The ground electrode was always positioned somewhere between the stimulus and the recording sites. Thus, for orthodromic pick-up, it was placed on the dorsal side of the forearm proximal to the site of median nerve stimulation. For the antidromic site of third digit, the ground electrode was fixed on the dorsum of the hand. For all the electrodes, viz. the stimulating, the recording and the ground electrodes, a small amount of electrode gel was used as conductive medium. The stimulating electrode pair was positioned longitudinally over the median nerve at the wrist with the cathode proximal and held in place by velcro strap. To pick up the brachial plexus response, the electrode was attached to the skin of the supraclavicular fossa and was held in position by adhesive plaster. The Erb's point and the cortical potentials were acquired with midline forehead (FZ) as reference.

3.3 NORMAL DATA COLLECTION.

Figures 3.2 to 3.5 are photographs showing the recording in progress to obtain the responses to median nerve stimulation at the four different pick up sites. Twenty five normal subjects were selected from the students, the faculty and the departmental staff of this Institute. Twenty three of them were in the age

group 19 - 31 with mean age of 24.9 years and a mean height of 163.9 cm. None of them had a history of neurological problems. The testing was carried out in a quiet room with the subject fully relaxed in a reclining chair with the leg supported appropriately to minimize muscle activity. The subject was made to sit one metre away from the computer to reduce power line frequency interference. The skin of the stimulating and recording sites was cleaned by rubbing with cotton soaked in ethyl alcohol to remove dead epithelial cells and other dirt and thus to reduce the electrode-skin interface impedance. Then the electrodes were fixed with necessary conductive paste. Square wave pulses of 100 microseconds duration were applied at a rate of one per second to identify the stimulus strength required. The intensity and the stimulus electrode position were adjusted to effect a minimal thumb twitch at minimal voltage. The stimulus threshold having been identified, averaging was started at two stimuli per second. With such low voltages, repetitive stimulation at two per second is not painful or uncomfortable. In fact, some of the subjects were so relaxed that they tended to sleep while the acquisition of data was in progress ; however, they were not allowed to sleep to prevent any possible alterations in the central conduction due to the sleep states. Actual recording, however, was done with a stimulus repetition period of 510 msec. This value of inter-stimulus interval ensures that the supply frequency noise, if present, is out of phase in successive sweeps, so that it cancels itself. In other words, whatever the value of stimulus rate selected, the corresponding inter-stimulus interval is slightly changed such that it is (2n + 1)/2 times the mains period. Thus

the effect of supply interference is eliminated through an ingenious choice of stimulus repetition frequency.

Activity was recorded in a bipolar fashion and the amplifier gain was automatically adjusted by the system to bring the signal level to slightly below the input range of the analog to digital converter. Filter passband was 10 - 1000 Hz (3dB down) for all the peripheral and central recordings. Notch filter was not used in any of the recordings to preserve the actual frequency contents in the signal. Whenever excessive artifact was present, that particular sweep of data was automatically rejected by the program and the reject count incremented and displayed on the monitor. In almost all the cases, the number of rejected sweeps was less than 5% of the total number of sweeps averaged. The sweep of the averaging computer was started immediately after the delivery of the stimulus with zero delay.

Sixteen sweeps were averaged in the case of nerve conduction potentials at the digit and the elbow, sixty four sweeps in the case of Erb's point potential and 128 or 256 sweeps for the cortical potential. Activity was recorded for 20 msec at the rate of 16.66 KHz (samples at 60 μsec equal intervals) for the compound nerve action potentials(CNAPs) and for 40 msec at the rate of 7.5 KHz (samples at 133.3 μsec equal intervals) for the EPs. Potentials at each point were recorded twice by performing two complete trials to ensure the correctness and repeatability of the recorded waveforms. The whole test with all four recordings was then repeated on the median nerve of the other

hand for three normals. The complete test took an average of 120 minutes to perform. Once the necessary numbers of noise free sweeps have been acquired, the averaged data was first stored on a floppy disk and then displayed on the monitor. The software, while saving a waveform on the floppy drive, saves also all the parameters, viz. sweep details, number of stimuli, number of rejects and the gain of the amplifier. Figs. 3.6 through 3.9 (panel a) show responses from a normal taken at the four recording sites.

3.4 PATIENT DATA COLLECTION

For patient data collection, the entire evoked potential averaging system was moved to the leprosy hospital. Twenty one patients were studied for investigating the extent of neurological damage. Sixteen of them were in the age group of 20-33 (mean 25.1 years) with a mean height of 160.0 cm. Most of them had a disease history of two years and more (mean 5.7 years and range 1 - 15 years) and a number of them have been taking drugs recommended by the hospital for a period of one year minimum (mean 3.4 years and range 0.3 to 10 years). During the collection of the data from patients on various days, the room temperature varied between 29° C and 32° C. None of the patients studied had fever or any other health problem which affected their body temperature. For all the patients, responses were obtained from either side of the body, by stimulating the left and right median nerves separately irrespective of whether or not both the upper limbs were clinically judged to be affected. Figs. 3.6 to 3.9 (panel b) illustrate a set of potentials recorded after

stimulation of left median nerve of a leprosy patient.

The age, height and the motor threshold stimulus voltage were all noted for the patients as also for the normal subjects. The lengths of the arm segments between the stimulus site and each of the three peripheral recording sites were measured and noted to enable the calculation of segmental conduction velocities. From the patient files maintained by the physiotherapy department, the clinical evaluation of the patients regarding the sensory and the motor damage in the upper limbs were recorded. Areas of partial or total loss of sensation, paresis, paralysis or anaesthekinesia, locations of active and healed patches, hand clawing if any, details regarding decompression of any nerve by surgical slitting of the nerve sheath, etc. were also noted, with a view to correlate the electrophysiological data with the clinical observations.

3.5 NOMENCLATURE USED

Figures 3.6 to 3.9 present and compare a set each of healthy and pathological potentials recorded after electrical stimulation of the left median nerve of a normal and a patient respectively. The placement of electrodes and the amplifier connections were made such that an upright deflection indicates a negative potential and a downward deflection indicates a positive potential. By convention, the evoked potential peaks are named by their polarities and latencies. Thus, the negative brachial plexus peak which occurs around 9 to 10 msec is known usually as N9 and the following positive wave is referred to as P11 (see

Fig.3.8). Similarly, the negative potential in the somatosensory cortical response appearing around 19 mec is normally called N19 and the immediately next pósitive deflection is generally designated P22 (refer Fig.3.9). Though there are no such commonly accepted terms for the peripheral responses, the same convention has been used by the author in naming these potentials too. Thus, for the purpose of convenience in reference hereafter in this thesis, the negative and positive peaks in the digital and forearm responses are designated N3, P4 and N5, P6 respectively (refer Figs. 3.6 and 3.7). A list of notations and abbreviations used in the thesis is given at the end of the thesis.

The x-axis in all the figures (3.6 to 3.9) is time in msec reckoned from the instant of stimulation. The x-scale is the same for all the four potentials and is equal to 4 msec per division. The y-axis is the absolute amplitude of the waveforms in microvolts. The scale in the y-axis is different for different waveforms depending upon the amplitude of the corresponding response and the actual value is printed on the top left hand corner of the respective waveforms. In the case of the three peripheral potentials, the nerve conduction times(NCT) and the nerve conduction velocities (NCV) have also been printed along with the waveforms. The values printed below the records are, respectively, the absolute latencies and amplitudes of the largest negative (upward) peak, the immediately following positive peak and the interpeak latency and the difference in amplitude between these two peaks. Each response is identified by an alphanumeric code of length 8, formed such that the first 3

letters refer to the subject's name, the next 2 indicating whether it is right or left median response(RM/LM), the subsequent 2 letters identifying the site of recording (DG for digit, LB for elbow, RB for Erb's point and SC for scalp) and the final digit indicating the number of the trial for that response.

3.6 CONCLUSION

Electrophysiological data were obtained from the upper limbs of 21 Hansen's disease patients in order to study the extent of peripheral nerve damage and also to examine whether there was any involvement of the central nervous system also. In order to evaluate the data against normal neural responses, event related potential and nerve conduction data were obtained from 25 healthy youth as well.

The plots of neural potentials for normal and patient are given as an example only. The details are discussed in Chapter 4.

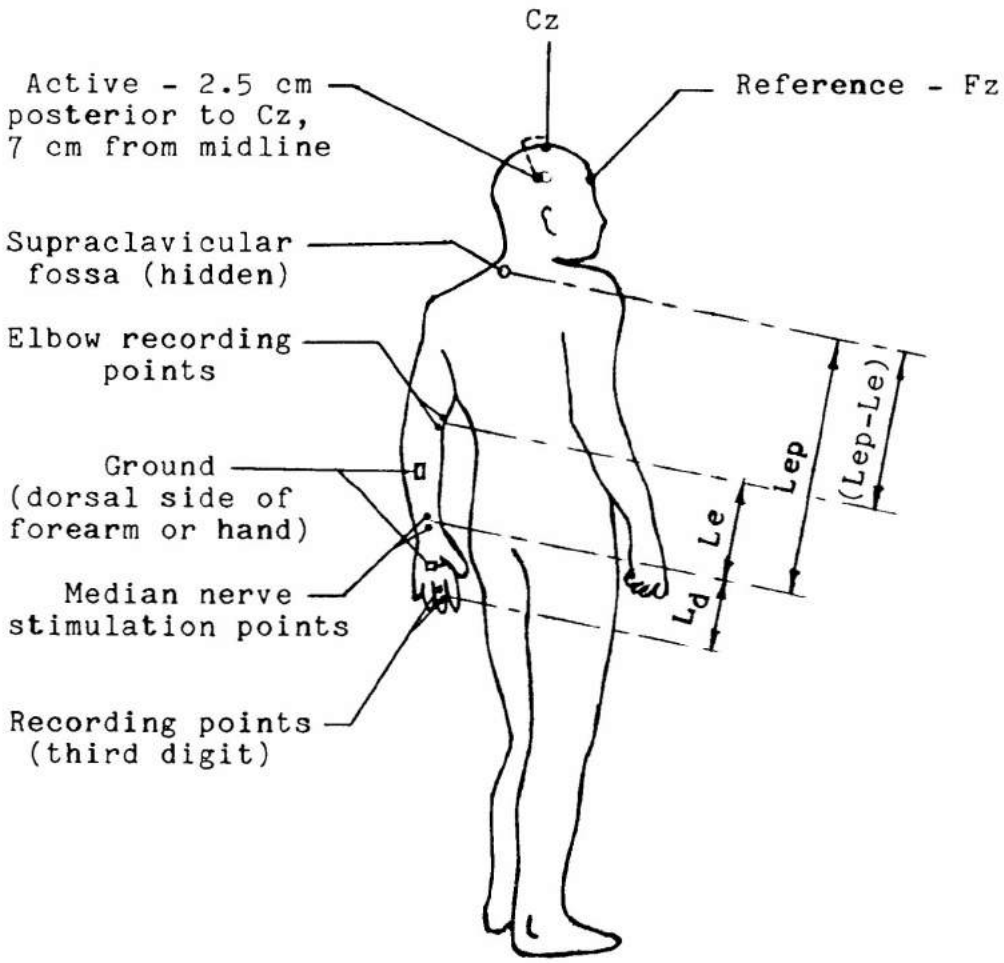


FIG. 3.1 STIMULATION AND RECORDING SITES USED IN THE STUDY
(the lengths of the nerve segments have been marked for each recording site)

Fig.3.2. Recording of CNAP in progress from third digit - median nerve stimulation at wrist.

Fig.3.3. Recording of CNAP in progress from elbow site - median nerve stimulation at wrist.

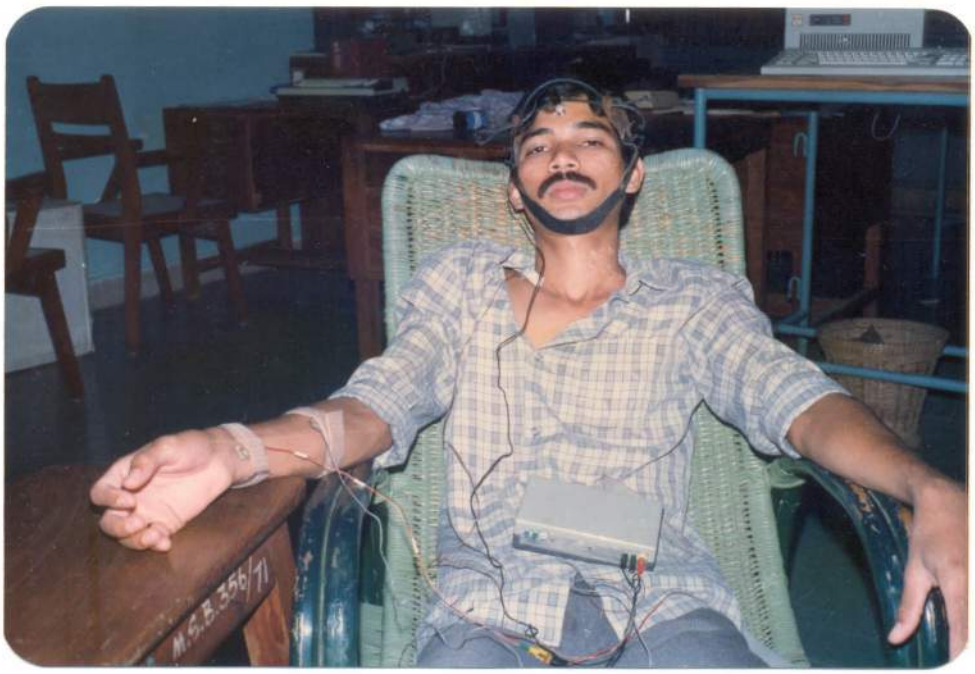


Fig.3.4. Recording of brachial plexus response in progress - median nerve stimulation at wrist.

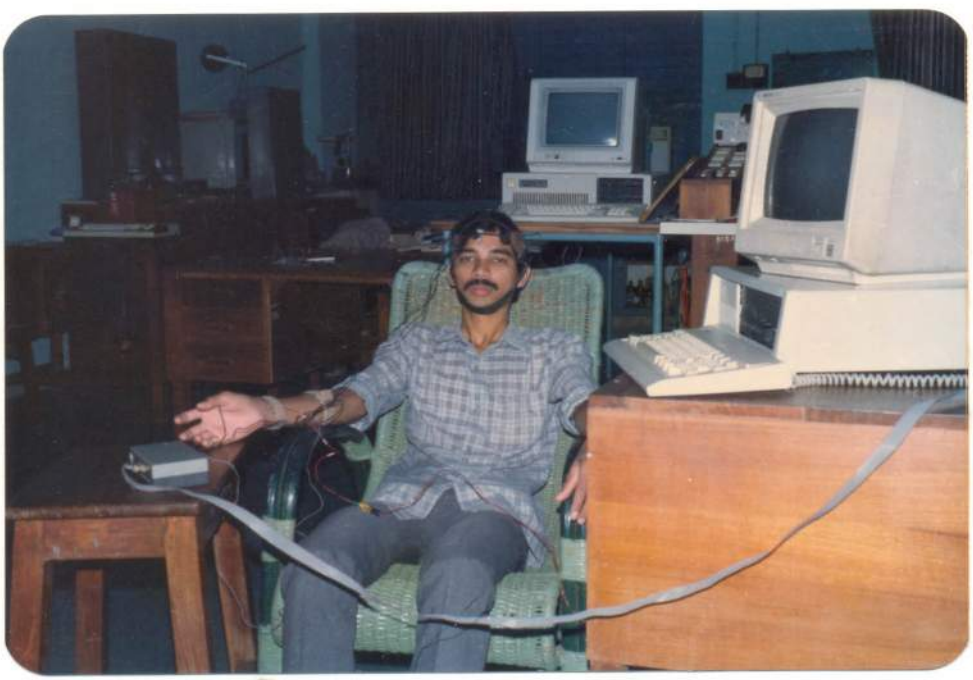
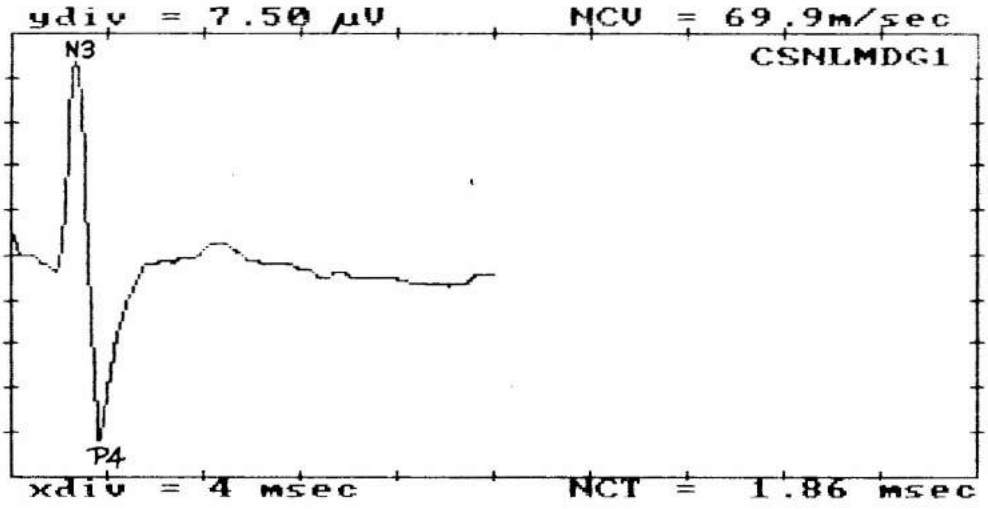
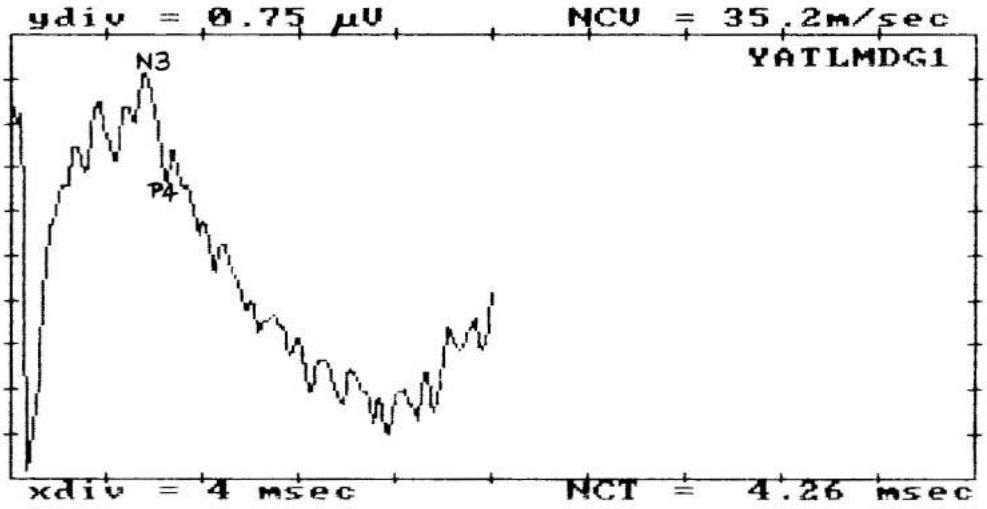


Fig.3.5. Recording of somatosensory evoked potential in progress - median nerve stimulation at wrist.



Peak	lat(msec)	ampl(μV)
N3	2.70	-38.037
P4	3.72	29.028
P4-N3	1.02	67.065

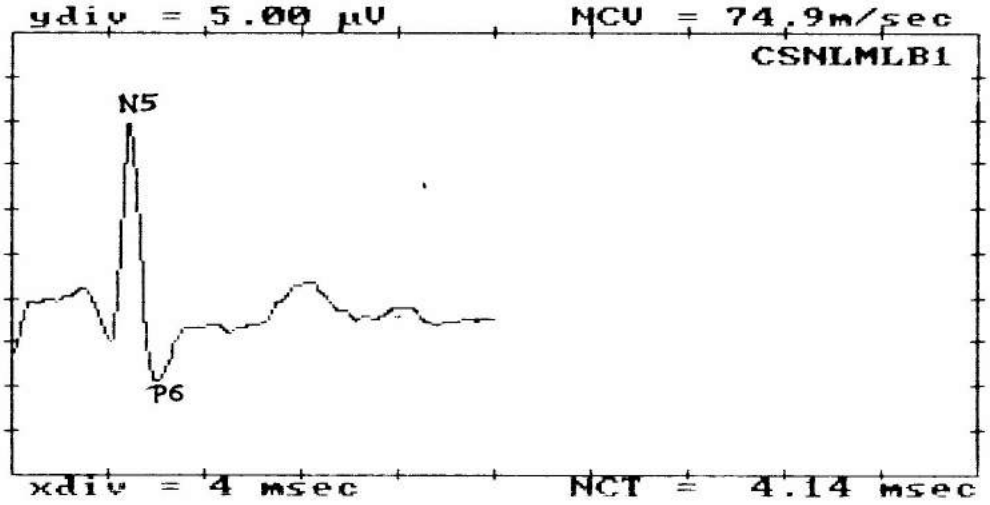
3.6.a. Response from a normal



Peak	lat(msec)	ampl(μV)
N3	5.52	-3.866
P4	6.48	-1.802
P4-N3	0.96	2.064

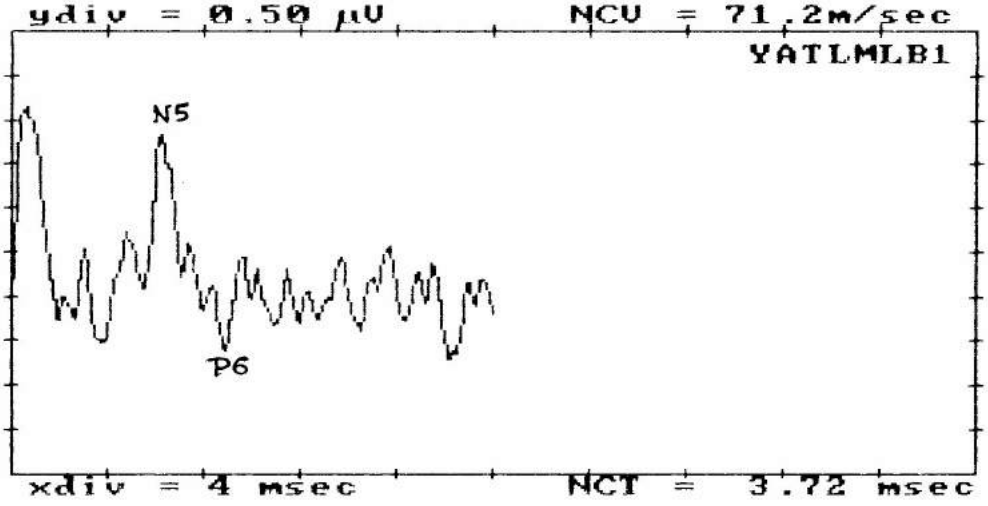
3.6.b. Response from a patient

Fig.3.6 CNAPs recorded from the third digit



Peak	lat(msec)	ampl(µV)
N5	4.92	-22.005
P6	5.94	7.422
P6-N5	1.02	29.427

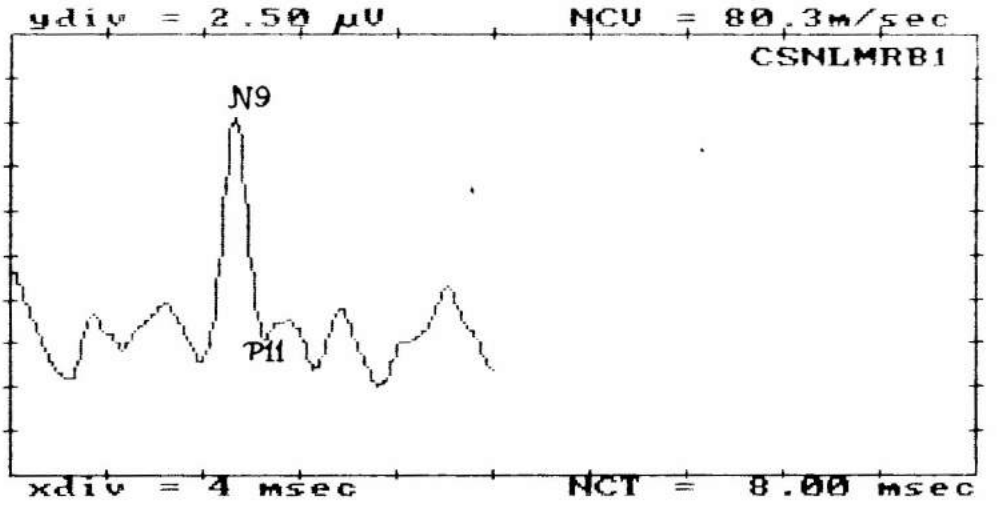
3.7.a. Response from a normal



Peak	lat(msec)	ampl(µV)
N5	6.30	-2.029
P6	8.94	0.535
P6-N5	2.64	2.563

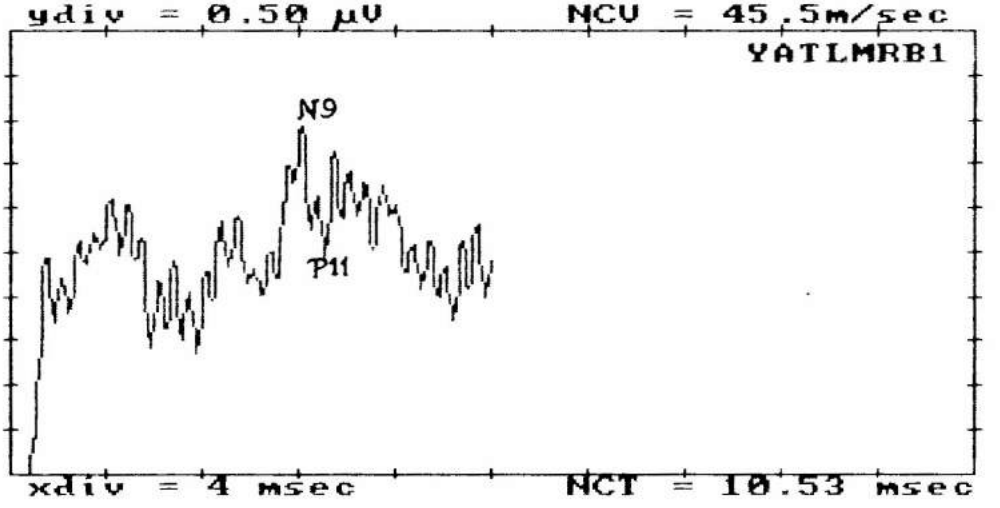
3.7.b. Response from a patient

Fig.3.7 CN4Ps recorded from the elbow



Peak	lat(msec)	ampl(μV)
N9	9.33	-12.500
P11	10.60	0.220
P11-N9	1.27	12.720

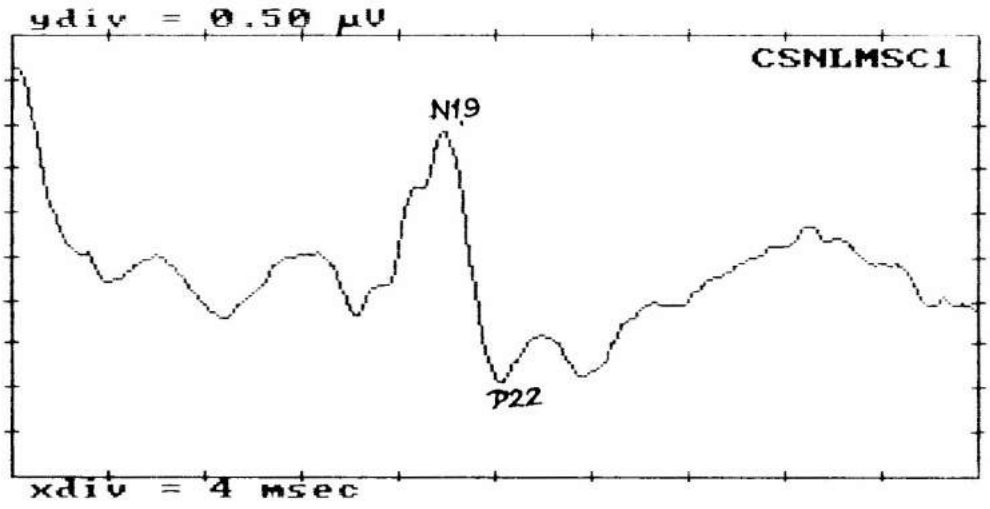
3.8.a. Response from a normal



Peak	lat(msec)	ampl(μV)
N9	12.20	-2.979
P11	13.13	-1.318
P11-N9	0.93	1.660

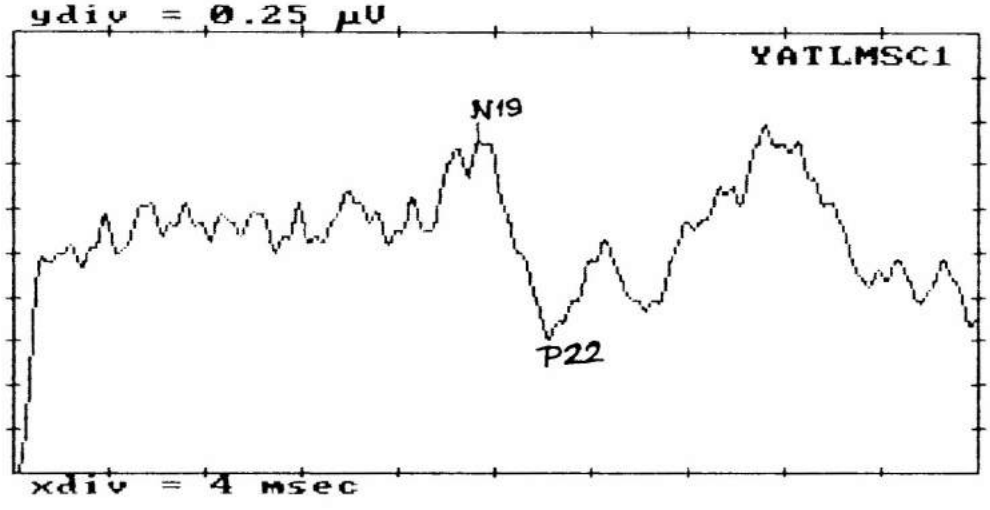
3.8.b. Response from a patient

Fig.3.8 EPs recorded from the Erb's point



Peak	lat(msec)	ampl(µV)
N19	17.83	-2.295
P22	20.17	0.742
P22-N19	2.33	3.037
N19-N9	8.50	

3.9.a. Response from a normal



Peak	lat(msec)	ampl(µV)
N19	19.33	-1.611
P22	22.27	-0.195
P22-N19	2.93	1.416
N19-N9	7.13	

3.9.b. Response from a patient

Fig.3.9 SEPs recorded from the scalp

4. TIME DOMAIN ANALYSIS

4.1 INTRODUCTION

During the data acquisition phase, the responses from healthy and diseased subjects were recorded without any smoothing or further processing. All analyses were done off-line. In the case of time domain analysis, the stored waveforms were once again displayed on the monitor and necessary measurements were carried out by means of a vertical line cursor moving along the horizontal direction. The cursor appears as soon as the waveform is displayed on the screen. The amplitude and the latency values of the waveform at the cursor position are also displayed. Since the gain setting of the amplifier is also recorded when the data is stored, the displayed amplitude is the actual magnitude of the signal in microvolts. When the cursor is moved, the amplitude and latency displays also change and show the instantaneous values. Thus, peaks can be unambiguously identified and their attributes read off. The system has provision to mark a peak and the following valley, and then to read the difference in amplitude and latency. This facility enables measurement of the amplitude and duration of a potential. The system also facilitates computation of interpeak latencies with reference to a particular peripheral latency. This is achieved by taking the cursor to the peak of interest, pressing a key and then entering the latency value of the reference peak. Nerve conduction velocity(NCV) measurements are similarly done by taking the cursor to the point where the conducted impulse just reached the site of recording, and then pressing another key, and subsequently entering the

conduction distance. The value of NCV appears on the screen and is noted.

4.2 ABSOLUTE AND RELATIVE LATENCY MEASUREMENTS

The minimum stimulus voltage required to effect a thumb twitch was made note of in all the cases. The absolute latencies of the main negative peaks (N3, N5, N9 and N19) of all the four responses were read off the respective waveforms on the screen and noted. Table 4.1 lists the sex, age, height, stimulus threshold and the absolute latencies of the responses of the normal subjects studied. The values obtained in the case of the patients are tabulated in Table 4.2. For each patient, there are two entries under each column in the table; top entry corresponds to the right arm values and the bottom one, to the left arm values. Table 4.2 also lists the mean, standard deviation and the spread of the data for both normals and patients.

The data from patients were divided into two groups: (i) data from those upper limbs (marked in Table 4.2 by a '*' preceding the patient ID) with clinical evidence of median nerve abnormality in the form of enlargement or tenderness or pain or associated muscle weakness and (ii) data from upper limbs with no clinically observable median nerve abnormality. Thus, it is possible that data from one side of a patient was added to group(i) and that from the other side was added to group(ii), depending upon the clinical symptoms of the individual median nerves. This distinction was made in order to observe whether there are any definite changes in the response of the nerve prior

to the clinical manifestation of dysfunction. Accordingly, Table 4.2 lists separately the statistics of the two groups. The significance of the difference between the means for normals and for each of the two groups was determined for each latency. The p values are also tabulated. Some of the responses could not be recorded from three upper limbs of two patients. Hence, the data from those limbs (marked in Table 4.2 by a '!' preceding the patient ID) were not included in either group for computing the statistics.

Also calculated were the interpeak latencies (P4-N3, P6-N5, P11-N9, P22-N19) of the response peaks (time intervals between the main negative peaks and the following positive peaks). The Central Conduction Time(CCT), being the difference between the N19 cortical potential latency and N9, the latency of the brachial plexus component was computed for all the cases. These values for the normals and patients are given in Tables 4.3 and 4.4 respectively.

4.3 COMPUTATION OF THE CONDUCTION VELOCITIES

The nerve impulse arrival times(nerve conduction times, NCT) at the three peripheral recording sites were read off the screen from their respective waveforms. The actual lengths of the nerve segments between the electrode sites were measured in each patient and the nerve conduction velocities were computed by dividing these distances by the respective segmental conduction times. In case of the arm segment, the length of the nerve involved is the difference between the distances of the two

recording sites, namely, elbow and Erb's point, from the wrist. Referring to Fig. 3.1, this segmental length can be identified as (Lep-Le). This length is divided by the corresponding segmental conduction time to arrive at the value of NCV (Va). This conduction time is the difference in arrival times of the propagating nerve impulse at brachial plexus (NCT,arm) and elbow(NCT,forearm). Tables 4.5 and 4.6 list the nerve conduction times and the segmental conduction velocities of normals and patients respectively.

4.4 MEASUREMENT OF AMPLITUDES

The peak to valley amplitudes of the compound nerve action potentials at the finger (Ad = P4-N3) and elbow (Ae = P6-N5) were measured and tabulated. Similarly, Ab(P11-N9) and As(P22-N19), being the peak to peak amplitudes of the waveforms recorded at Erb's point and scalp respectively were measured and tabulated. Table 4.7 shows the individual amplitudes of the responses from the control subjects. The sample statistics of each of the 4 responses were calculated for all the 3 sets of data (normals, clinically abnormal limbs and clinically normal limbs). The amplitudes of the patient responses, the sample statistics and the significance of deviation of patient data from normal data are all listed in Table 4.8.

4.5 RESULTS AND DISCUSSION

It is observed that both the sensory and motor thresholds of the median nerve are appreciably higher in patients. The

increase in the stimulus threshold is statistically significant ($p<.005$) in both the groups of patient data. A look at the mean values of the absolute latencies reveals that it is only the distal latency N3, which is considerably prolonged in the case of the patients ($p<.001$ in both groups). The increase in N5 is not at all significant. The changes in N9 and N19 latencies, though significant in the patient group 1($p<.005$ and $<.05$ respectively), are not significant in the other group (clinically unaffected). There is no appreciable difference between the normals and patients with respect to the mean values of the fall times of the potentials at any of the four recording sites, but the spread of values is large for patients.

There is significant reduction in the NCVs of all the three segments. Even in the clinically normal set, the decrease is highly significant ($p<.005$) for the palm segmental velocity(Vp) and very highly significant ($p<.001$) for the forearm segmental velocity(Vfa). A comparison between Tables 4.7 and 4.8 clearly shows that the magnitudes of all the three peripheral potentials are considerably lower in the case of patients than in the case of normals. The mean peak to peak amplitudes of the responses at the digit, elbow and the Erb's point in the case of the clinically abnormal group are 8.5%, 24.6% and 55.0% respectively of the corresponding values for the normals ($p<.001$ in each case). The values for clinically unaffected group are 27.2% for Ad and 60.1% for Ae and are both again very highly significant ($p<.001$). These results are pictorially represented in Fig.4.1.

A significant observation is that the amplitude of the scalp

EP is not appreciably different from the normal value(84.5%) even in the clinically affected group and the mean central conduction time is almost the same for both normals and patients. This presents an experimental verification for the fact that the Central Nervous System (CNS) is not affected in leprosy. The marginal decrease in the average amplitude of the scalp EP in the clinically abnormal cases is attributed by the author to less excitation reaching the CNS from the brachial plexus (where the amplitude of the nerve impulse is significantly less than that for normals). The marginal increase in the clinically normal cases is mainly due to the inclusion of the very high values of a young patient (PV, age 15, see Table 4.8 for values).

4.5.1 Clinical correlation

The clinical assessment from the patient records was correlated with the neurophysiological data obtained. Three cases are illustrated here as examples. The patient PX has near total loss of sensation in the distal segment upto a distance of 10 cm proximal to wrist of both hands. Assessment of muscle power shows that right median nerve is normal and there is lower median nerve paresis in the left hand. The fact that there is total loss of sensation in the left hand is not reflected in the conduction velocity of the palm segment(see Table 4.6), which has a perfectly normal value, whereas the amplitudes of the peripheral potentials are very low and the values are marginally higher in the case of the right hand (see Table 4.8) and thus correlate well with the clinical observations. The patient PXIII is one who

has been fully cured of the disease and he has some residual lower ulnar motor weakness in the right hand whereas the median nerve innervated motor and sensory activities are fully normal in the left upper limb. Here, the right arm distal conduction velocity (see Table 4.6) is in the abnormal range. The amplitudes of both distal peripheral potentials (see Table 4.8) are totally in the normal range. Considering the other case, patient PXX has no sensations distal to wrist in the left hand while the motor activity is normal. In the right arm, though the median nerve is thickened, there is neither sensory loss nor any motor weakness. The right arm digital response amplitude of 25.7 μV (see Table 4.8) is less than the minimum normal value (mean - S.D.) of 31.5 μV and higher than the maximum in the patient range(mean + S.D.) of 18.7 μV whereas the value of left arm potential is only 2.051 μV. Similar difference is seen with elbow values also. On the other hand, the left arm palm NCV (see Table 4.6), though less than the right side, is almost a normal value and gives a misleading picture if one goes by it.

4.6 CONCLUSION

The changes in the absolute and relative latencies of the peaks in the various responses are not statistically significant. Thus, these parameters are not useful in reflecting the abnormalities of patient responses. Trying to relate the nerve conduction velocities with the clinical findings has not revealed any significant correlation, whereas there is nearly perfect correlation between the amplitudes of the compound nerve action potentials and the motor or sensory deficits observed clinically.

The normal range of palm NCV(mean ± S.D.) is 59.7 m/sec to 74.3 m/sec. The ranges of patient values are 41.1 m/sec to 62.9 m/sec for the clinically affected group and 46.8 m/sec to 68.6 m/sec for the other group. Thus there is an overlap in the ranges and hence discrimination based upon NCV alone cannot be error-free, though the reduction in both the distal NCVs is highly significant. However, in the case of the amplitudes of the digital compound nerve action potentials, there is a clear margin of around 21 μV and 7 μV between the normal range and the two abnormal ranges. Again, there is a margin of around 5 μV between the ranges of elbow amplitudes between controls and the clinically affected group. Hence the distal amplitudes are reliable indicators of the abnormality of the nerve. These detailed studies revealing the relative advantage of the amplitudes over the velocities have not been carried out so far and hence, constitute an important method of early detection of leprosy.

That the leprosy bacilli do not infect the CNS is revealed by the normal features of the cortical potentials. The overall reduction, consistently seen in the amplitudes of the peripheral potentials implies a considerable reduction in the number of active, fast-conducting sensory nerve fibres. The significance values as well as the ranges of the parameters as shown by Fig.4.1 underline the importance of the changes in the two distal potentials even in the clinically normal group. Thus, to screen an exposed population in a short time, it will suffice to record only the digit and elbow responses in both the hands to median

nerve stimulation at the wrist and evaluate the subjects based on the amplitudes, NCVs and the stimulus thresholds. If there is an order of magnitude difference between the left and right side, or if any of the values is much below the normal range, then such cases can be referred to the leprosy centres for smear tests, biopsy and so on to establish the presence or absence of infection by mycobacterium leprae.

TABLE 4.1 - STIMULUS THRESHOLDS AND ABSOLUTE LATENCIES - NORMALS

SUBJ. ID	SEX	AGE Yrs	HT. cm	STIM S,V	N3 msec	N5 msec	N9 msec	N19 msec
NI	M	45	165	38	2.76	4.62	8.87	18.00
NII	M	28	180	36	2.82	4.86	9.60	18.33
NIII	M	23	158	28	2.52	4.50	9.42	18.00
NIV	M	27	168	36	2.70	4.92	9.33	17.83
NV	M	21	172	24	2.58	4.92	10.87	19.50
NVI	M	29	165	38	2.76	4.68	9.53	18.50
NVII	M	28	175	57	2.82	4.92	10.93	19.83
NVIII	M	26	180	22	2.93	5.13	10.80	19.60
NIX	M	24	171	36	2.46	5.58	11.07	19.83
NX	M	28	165	22	2.64	5.10	9.84	18.83
NXI	M	48	162	34	2.52	5.04	9.90	19.17
NXII	M	26	180	20	2.80	4.47	9.67	18.53
NXIII	F	23	154	34	2.10	4.38	8.53	16.67
NXIV	M	26	170	39	2.64	4.50	9.66	18.33
NXV	F	26	155	40	2.82	4.92	9.33	18.17
NXVI	F	22	149	32	3.24	4.86	9.27	17.17
NXVII	F	24	168	48	3.12	5.10	10.20	18.50
NXVIII	F	31	154	34	2.88	4.50	9.27	18.67
NXIX	F	19	159	32	3.06	4.68	9.33	18.00
NXX	F	23	157	34	2.64	4.92	9.60	18.00
NXXI	F	21	155	45	2.58	4.26	9.07	17.83
NXXII	F	23	158	34	2.58	4.86	9.07	18.33
NXXIII	F	22	151	34	2.58	4.50	9.00	19.50
NXXIV	F	28	164	38	2.64	4.86	9.40	18.33
NXXV	F	25	161	22	2.64	4.74	9.33	17.83

TABLE 4.2 - STIMULUS THRESHOLDS AND ABSOLUTE LATENCIES - PATIENTS

PAT. ID	SEX	AGE Yrs	HT. cm	STIM. S,V	N3 msec	N5 msec	N9 msec	N19 msec
PI -R	M	23	157	60	3.24	4.62	9.40	16.93
-L				40	3.18	4.20	8.40	16.67
*PII	M	26	160	96	3.30	5.70	11.00	20.53
				38	3.36	4.44	9.67	18.13
*PIII	M	20	153	40	3.36	4.50	9.00	18.53
*				45	3.36	4.50	8.80	17.33
!PIV	M	25	165	115	NR^	5.10	10.93	19.20
				76	5.52	6.30	11.60	18.53
PV	M	15	147	35	3.18	4.32	10.80	17.33
*				26	5.52	4.38	10.80	17.73
*PVI	M	25	158	80	3.12	5.16	9.80	17.83
				65	3.42	4.98	9.53	18.27
PVII	M	25	168	38	5.16	5.46	10.20	19.33
*				25	5.70	5.52	11.20	22.67
*PVIII	M	40	170	57	3.96	6.00	11.33	21.83
*				57	3.42	5.70	11.17	19.73
PIX	M	23	162	51	2.88	5.10	9.83	18.67
*				51	2.76	5.04	9.50	18.50
*PX	M	23	150	66	3.78	5.94	13.73	21.67
*				57	3.90	5.10	10.40	17.17
PXI	M	43	161	60	3.36	5.22	10.80	19.20
				57	4.02	5.34	10.87	19.20
*PXII	M	27	185	47	3.72	5.40	11.60	20.53
*				56	5.40	5.46	14.13	22.40
PXIII	M	21	164	28	3.18	4.80	9.53	17.33
				38	3.00	5.10	9.33	17.73
*PXIV	M	32	165	62	3.36	4.98	10.17	19.83
				40	3.12	5.04	9.83	19.17
PXV	M	60	163	68	3.24	4.80	10.00	19.33
				86	3.18	4.86	9.83	18.50
PXVI	M	33	149	81	3.72	5.10	9.83	18.17
				38	3.78	4.26	9.67	18.67

^ NR : No response

TABLE 4.2 - STIMULUS THRESHOLDS AND ABSOLUTE LATENCIES - PATIENTS - contd.

PAT. ID	SEX	AGE Yrs	HT. cm	STIM. S,V	N3 msec	N5 msec	N9 msec	N19 msec
PXVII-R	M	22	150	48	3.84	4.92	9.17	17.17
-L				21	3.60	4.38	9.17	16.83
*PXVIII	F	25	152	36	3.60	4.62	9.33	18.00
*				36	2.64	4.68	9.17	17.83
!PXIX	M	43	171	86	NR ^	8.04	11.00	19.50
!				102	NR	6.66	NR	20.17
PXX	M	30	170	45	3.60	5.64	11.73	19.73
*				164	3.48	3.48	11.20	18.67
PXXI	M	21	152	40	3.66	4.74	9.53	18.53
				45	3.60	4.56	9.00	17.07
NORMALS :								
MEAN		25	164	34	2.72	4.79	9.66	18.44
STD.DEV.		3	9	9	0.23	0.29	0.66	0.79
RANGE		19	149	20	2.10	4.26	8.53	16.67
		to	to	to	to	to	to	to
		31	180	57	3.24	5.58	11.07	19.83
PATIENTS [MEDIAN NERVE CLINICALLY AFFECTED LIMBS(17)] :								
MEAN		25	160	59	3.79	5.07	10.73	19.46
STD.DEV.		4	9	32	0.88	0.64	1.46	1.79
RANGE		20	149	25	2.64	3.48	8.80	17.17
		to	to	to	to	to	to	to
		33	185	164	5.70	6.00	14.13	22.67
p				.005	.001	N/S ~	.005	.05
PATIENTS [MEDIAN NERVE CLINICALLY UNAFFECTED LIMBS(22)] :								
MEAN				50	3.58	4.92	9.90	18.20
STD.DEV.				17	0.63	0.49	0.80	0.92
RANGE				21	2.88	4.20	8.40	16.67
				to	to	to	to	to
				86	5.52	6.30	11.73	19.73
p				.001	.001	N/S	N/S	N/S

^ NR : No response. ~ N/S : not statistically significant.
'*' denotes limbs with clinically affected median nerves.
'!' denotes limbs not included for statistics.

TABLE 4.3 - RELATIVE LATENCIES AND CCT OF NORMALS

SUBJ. ID	P4-N3 msec	P6-N5 msec	P11-N9 msec	P22-N19 msec	N19-N9 C.C.T. msec
NI	0.96	1.08	1.46	2.17	9.13
NII	0.96	1.02	2.33	2.50	8.73
NIII	1.08	1.26	1.50	5.33	8.58
NIV	1.02	1.02	1.27	2.33	8.50
NV	0.90	1.56	1.80	3.33	8.63
NVI	0.84	1.20	2.33	5.83	8.97
NVII	1.14	1.02	1.20	3.67	8.90
NVIII	1.13	0.93	0.93	3.47	8.80
NIX	0.84	1.14	1.67	5.67	8.76
NX	0.90	0.84	1.26	2.83	8.99
NXI	1.02	1.08	1.02	5.00	9.27
NXII	1.00	0.87	1.53	2.40	8.86
NXIII	0.90	1.14	1.13	3.00	8.14
NXIV	0.72	0.78	1.32	2.50	8.67
NXV	0.96	1.20	2.07	2.67	8.84
NXVI	1.32	1.38	2.07	3.50	7.90
NXVII	1.14	0.90	1.73	2.50	8.30
NXVIII	1.14	0.96	1.53	1.50	9.40
NXIX	1.14	0.96	2.13	3.00	8.67
NXX	0.90	1.38	1.73	2.50	8.40
NXXI	0.96	0.78	1.20	5.17	8.76
NXXII	0.96	0.96	1.33	2.33	9.26
NXXIII	1.02	1.02	0.53	1.17	10.50
NXXIV	0.90	1.20	1.73	2.50	8.93
NXXV	0.84	1.26	1.53	2.33	8.50

TABLE 4.4 - RELATIVE LATENCIES AND CCT OF PATIENTS

PAT. ID	P4-N3 msec	P6-N5 msec	P11-N9 msec	P22-N19 msec	N19-N9 C.C.T. msec
PI -R	1.14	1.02	1.13	2.14	7.53
-L	0.96	1.08	1.67	2.80	8.27
PII	0.90	3.48	1.60	3.07	9.53
	1.08	1.32	1.06	3.47	8.46
PIII	0.60	0.54	2.47	1.74	9.53
	0.84	1.02	1.73	2.94	8.53
PIV	NR ^	1.98	1.00	3.07	8.27
	0.96	2.58	1.07	3.47	6.93
PV	0.78	1.14	2.67	3.47	6.53
	0.78	1.26	3.13	3.47	6.93
PVI	0.48	1.02	1.60	1.00	8.03
	0.96	1.08	1.00	1.73	8.74
PVII	1.02	1.44	1.67	2.17	9.13
	0.96	0.78	0.33	1.83	11.47
PVIII	1.14	1.50	3.00	2.33	10.50
	0.42	1.08	1.67	3.73	8.56
PIX	0.90	0.96	1.00	4.33	8.84
	1.02	1.02	1.17	4.67	9.00
PX	0.66	0.78	3.00	0.50	7.94
	0.36	1.50	0.87	1.00	6.77
PXI	0.54	0.66	0.40	4.93	8.40
	1.14	1.56	1.87	3.47	8.33
PXII	0.90	1.26	1.73	4.93	8.93
	0.90	1.38	1.73	3.07	8.27
PXIII	1.08	0.78	1.13	2.67	7.80
	1.02	0.78	2.14	2.94	8.40
PXIV	0.96	0.90	1.17	2.33	9.66
	1.14	1.08	1.67	2.50	9.34
PXV	0.90	1.44	1.50	2.83	9.33
	0.96	1.38	1.67	3.50	8.67
PXVI	0.84	1.62	1.67	2.83	8.34
	1.74	1.02	2.50	5.67	9.00

^NR : No response

TABLE 4.4 - RELATIVE LATENCIES AND CCT OF PATIENTS - contd.

PAT. ID	P4-N3 msec	P6-N5 msec	P11-N9 msec	P22-N19 msec	N19-N9 C.C.T. msec
PXVII -R	0.84	0.90	1.67	1.83	8.00
-L	0.96	1.20	0.33	2.33	7.66
PXVIII	0.66	0.66	1.00	2.83	8.67
	0.48	0.96	2.33	2.33	8.66
PXIX	NCR ^	2.52	1.83	0.83	8.50
	NCR	1.32	NCR	1.67	NC ~
PXX	1.26	0.90	1.07	3.07	8.00
	0.90	2.16	1.60	0.93	7.47
PXXI	1.38	0.96	1.27	2.40	9.00
	0.78	0.96	1.73	3.07	8.07
NORMALS :					
MEAN	0.99	1.08	1.56	3.13	8.78
STD.DEV.	0.13	0.20	0.44	1.23	0.49
RANGE	0.72 to 1.32	0.78 to 1.56	0.53 to 2.33	1.17 to 5.83	7.90 to 10.50
PATIENTS [MEDIAN NERVE CLINICALLY AFFECTED LIMBS(17)] :					
MEAN	0.76	1.25	1.77	2.51	8.73
STD.DEV.	0.22	0.67	0.77	1.24	1.16
RANGE	0.36 to 1.14	0.54 to 3.48	0.33 to 3.13	0.50 to 4.93	6.77 to 11.47
p	.001	N/S	N/S	N/S	N/S
PATIENTS [MEDIAN NERVE CLINICALLY UNAFFECTED LIMBS(22)] :					
MEAN	1.02	1.18	1.45	3.07	8.52
STD.DEV.	0.24	0.40	0.57	0.94	0.49
RANGE	0.54 to 1.74	0.66 to 2.58	0.33 to 2.67	1.73 to 5.67	7.66 to 9.34
p	N/S	N/S	N/S	N/S	N/S

^ NCR : not a clear response. ~ NC : not possible to compute.
(Upper values : Rt. hand ; lower values : Lt. hand)

TABLE 4.5 - NCT AND NCV OF NORMALS

SUBJ. ID	NERVE CONDUCTION TIMES			SEGMENTAL COND. VELOCITIES		
	PALM msec	FOREARM msec	ARM msec	PALM Vp,m/s	FOREARM Vfa,m/s	ARM Va,m/s
NI	1.62	3.78	7.67	76.6	76.7	73.4
NII	1.44	4.08	8.07	69.0	71.1	72.7
NIII	1.74	3.78	7.56	72.2	74.1	75.4
NIV	1.86	4.14	7.93	69.9	74.9	80.3
NV	1.98	4.50	9.33	70.7	66.7	64.4
NVI	1.92	3.84	8.13	71.4	78.1	76.9
NVII	2.22	4.02	9.27	58.6	79.6	61.8
NVIII	2.20	4.33	9.07	65.9	69.9	83.1
NIX	1.98	4.02	8.80	62.5	74.6	63.2
NX	1.98	4.20	8.46	70.7	73.8	74.9
NXI	1.92	4.02	8.40	72.2	74.6	68.5
NXII	2.07	3.67	8.20	73.1	81.3	75.5
NXIII	1.56	3.48	7.20	70.5	74.7	75.3
NXIV	1.92	3.72	8.40	72.9	75.3	70.5
NXV	2.10	4.20	8.13	61.9	69.0	73.7
NXVI	2.16	3.90	7.33	50.9	69.2	72.8
NXVII	2.34	4.14	8.53	55.6	77.3	56.9
NXVIII	2.34	3.66	7.60	55.6	76.5	78.7
NXIX	2.04	3.84	7.93	58.8	80.7	66.0
NXX	1.80	4.08	8.33	72.2	71.1	68.2
NXXI	1.92	3.48	7.87	62.5	80.5	61.6
NXXII	2.04	4.02	7.60	78.4	72.1	72.6
NXXIII	1.62	3.24	7.40	80.2	86.4	57.7
NXXIV	1.98	3.90	8.27	70.7	79.5	68.7
NXXV	2.04	3.90	7.87	66.2	79.5	70.6

TABLE 4.6 - NCT AND NCV OF PATIENTS

PAT. ID	NERVE CONDUCTION TIMES PALM msec	FOREARM msec	ARM msec	SEGMENTAL COND. VELOCITIES PALM Vp,m/s	FOREARM Vfa,m/s	ARM Va,m/s
PI -R	2.10	3.78	7.73	71.4	67.5	72.1
-L	2.28	3.54	7.40	70.2	71.8	75.3
PII	2.46	3.84	8.73	61.0	74.2	61.3
	2.52	3.84	7.13	58.1	72.8	57.7
PIII	2.88	4.14	8.07	52.1	58.0	77.7
	2.94	3.48	7.93	49.3	73.3	67.1
PIV	NR ^	3.66	7.87	NR	69.7	73.7
	4.26	3.84	10.07	35.2	69.0	53.0
PV	2.22	3.48	7.73	65.3	69.3	62.1
	4.86	3.60	9.47	28.8	65.6	47.0
PVI	2.82	3.90	8.67	46.1	70.5	55.6
	2.22	4.26	8.13	58.6	59.9	68.4
PVII	4.14	4.62	9.20	35.0	60.6	76.4
	4.08	4.68	10.53	35.5	59.8	59.8
PVIII	2.46	5.04	9.83	61.0	61.5	62.6
	3.18	4.62	9.50	47.2	67.1	63.5
PIX	2.16	4.32	8.17	69.4	69.4	80.6
	2.58	4.02	8.67	52.3	72.1	66.7
PX	3.06	5.28	11.40	47.4	62.5	49.0
	2.22	4.68	9.40	65.3	66.2	67.8
PXI	3.06	4.56	9.13	55.6	60.3	66.7
	3.78	4.44	9.27	43.7	61.9	61.1
PXII	3.06	4.14	8.07	58.8	72.5	91.6
	5.10	4.38	13.20	35.3	71.9	36.3
PXIII	2.46	3.90	7.93	54.9	73.1	66.9
	2.34	4.08	8.27	59.8	68.6	64.5
PXIV	2.22	4.44	8.67	67.6	63.1	78.1
	2.28	4.26	8.33	65.8	68.1	78.6
PXV	2.22	3.96	8.83	72.1	73.2	59.5
	2.16	4.02	8.83	74.1	67.2	64.4
PXVI	3.06	3.66	8.33	52.3	68.3	58.8
	3.30	3.48	8.17	45.5	63.2	67.2

^ NR : No response

TABLE 4.6 - NCT AND NCV OF PATIENTS - contd.

PAT. ID	NERVE CONDUCTION TIMES PALM msec	FOREARM msec	ARM msec	SEGMENTAL COND. VELOCITIES PALM Vp,m/s	FOREARM Vfa,m/s	ARM Va,m/s
PXVII-R	2.94	4.14	7.83	51.0	58.0	67.7
-L	2.46	3.66	8.33	61.0	65.6	53.5
PXVIII	2.34	3.78	8.33	64.1	62.2	62.6
	2.40	3.90	8.17	54.2	66.7	60.9
PXIX	NCR ^	5.94	9.50	NCR	53.9	75.8
	NCR	4.02	NCR	NCR	77.1	NCR
PXX	2.82	4.86	10.80	63.8	65.8	58.9
	3.06	3.30	10.13	58.8	90.9	49.8
PXXI	2.82	4.14	8.40	55.0	61.6	69.2
	2.82	3.84	8.47	51.4	66.4	62.8
NORMALS :						
MEAN	1.97	3.92	8.14	67.0	75.5	70.5
STD.DEV.	0.22	0.29	0.58	7.3	4.7	6.9
RANGE	1.44	3.24	7.20	50.9	66.7	56.9
	to	to	to	to	to	to
	2.34	4.50	9.33	80.2	86.4	83.1
PATIENTS [MEDIAN NERVE CLINICALLY AFFECTED LIMBS(17)] :						
MEAN	3.04	4.19	9.34	52.0	68.1	62.2
STD.DEV.	0.84	0.53	1.35	10.9	7.5	12.6
RANGE	2.22	3.30	7.93	28.8	58.0	36.3
	to	to	to	to	to	to
	5.10	5.28	13.20	67.6	90.9	91.6
p	.001	N/S ~	.001	.001	.001	.02
PATIENTS [MEDIAN NERVE CLINICALLY UNAFFECTED LIMBS(22)] :						
MEAN	2.75	4.03	8.48	57.7	66.4	65.7
STD.DEV.	0.63	0.37	0.83	10.9	4.5	7.4
RANGE	2.10	3.48	7.13	35.0	58.0	53.0
	to	to	to	to	to	to
	4.26	4.86	10.80	74.1	73.2	80.6
p	.001	N/S	N/S	.005	.001	.05

(Upper values : Rt. hand ; lower values : Lt. hand)

^ NCR : Not a clear response. N/S : not significant.

TABLE 4.7 - AMPLITUDES OF NORMAL RESPONSES

SUBJ. ID	P4-N3 Ad,μV	P6-N5 Ae,μV	P11-N9 Ab,μV	P22-N19 As,μV
NI	17.017	3.335	3.825	3.418
NII	18.485	8.522	7.666	4.443
NIII	81.775	15.777	3.552	4.319
NIV	68.311	28.866	12.134	2.637
NV	32.264	15.771	4.736	4.358
NVI	38.532	19.391	7.275	2.310
NVII	24.059	10.450	4.629	2.173
NVIII	30.225	17.188	3.145	2.019
NIX	52.319	8.972	8.154	4.785
NX	42.810	18.787	4.395	4.248
NXI	49.146	11.410	3.650	3.976
NXII	22.656	25.977	5.791	2.540
NXIII	91.040	14.893	8.985	5.046
NXIV	33.610	14.907	8.838	2.551
NXV	49.805	19.177	9.497	5.241
NXVI	64.990	17.057	7.015	4.766
NXVII	67.993	22.375	5.762	1.885
NXVIII	30.835	8.423	10.645	2.620
NXIX	43.213	21.077	12.500	2.539
NXX	55.225	23.926	9.351	3.262
NXXI	78.711	16.113	6.860	2.881
NXXII	47.900	18.848	9.595	2.232
NXXIII	63.281	16.797	3.516	3.345
NXXIV	78.516	16.048	7.446	2.883
NXXV	32.471	14.551	5.469	4.199

TABLE 4.8 - AMPLITUDES OF PATIENT RESPONSES

PAT. ID	P4-N3 Ad,μV	P6-N5 Ae,μV	P11-N9 Ab,μV	P22-N19 As,μV
PI -R	10.032	13.550	3.479	3.662
-L	12.574	18.665	9.888	2.881
PII	10.118	4.365	1.880	1.978
	7.325	5.824	3.345	2.454
PIII	14.966	1.709	2.747	2.800
	3.785	3.589	5.200	2.393
PIV	^NR	5.029	2.393	2.246
	2.009	2.363	2.222	2.758
PV	22.010	15.799	19.124	7.478
	0.733	9.121	11.475	7.117
PVI	1.379	6.730	3.443	1.416
	29.267	15.479	6.897	3.296
PVII	2.539	2.773	3.174	1.953
	1.116	0.381	0.854	3.198
PVIII	0.825	1.839	5.371	3.271
	2.087	0.977	3.027	2.100
PIX	14.637	12.109	5.322	4.346
	8.643	8.545	4.688	3.313
PX	1.289	2.490	3.955	0.781
	1.151	1.523	2.869	0.355
PXI	0.791	2.360	3.125	8.130
	3.950	4.629	3.882	3.296
PXII	2.490	5.225	3.857	3.125
	2.002	3.685	3.320	3.418
PXIII	34.717	19.434	11.353	5.030
	26.892	12.315	12.614	3.466
PXIV	9.351	11.646	4.150	3.369
	18.506	7.690	8.382	4.248
PXV	18.604	12.158	5.957	1.768
	15.332	7.373	8.203	3.483
PXVI	10.391	5.627	3.369	3.809
	6.323	3.675	2.686	3.092

(Upper values : Rt. hand ; lower values : Lt. hand)
^ NR : No response

TABLE 4.8 - AMPLITUDES OF PATIENT RESPONSES - contd.

PAT. ID	P4-N3 Ad, μV	P6-N5 Ae, μV	P11-N9 Ab, μV	P22-N19 As, μV
PXVII-R	7.959	12.549	5.469	5.469
-L	10.270	7.861	3.825	4.053
PXVIII	9.375	6.470	5.615	6.470
	0.698	2.415	3.744	2.262
PXIX	NCR^	1.413	3.223	0.212
	NCR	2.051	NCR	0.562
PXX	25.659	12.158	5.676	1.855
	2.051	0.842	1.660	0.928
PXXI	9.268	17.432	6.689	3.809
	10.754	14.746	5.029	7.259
NORMALS :				
MEAN	49.958	**17.126**	7.259	3.360
STD.DEV.	20.558	**5.124**	2.621	1.069
RANGE	18.485 to 91.040	8.423 to 28.866	3.145 to 12.500	1.885 to 5.241
PATIENTS [MEDIAN NERVE CLINICALLY AFFECTED LIMBS(17)] :				
MEAN	4.239	**4.209**	3.991	2.841
STD.DEV.	4.283	**3.191**	2.260	1.726
RANGE	0.698 to 14.966	0.381 to 11.646	0.854 to 11.475	0.355 to 7.117
p	.001	.001	.001	N/S
PATIENTS [MEDIAN NERVE CLINICALLY UNAFFECTED LIMBS(22)] :				
MEAN	13.628	10.299	6.350	3.982
STD.DEV.	9.139	5.364	3.941	1.715
RANGE	0.791 to 34.717	2.360 to 19.434	2.222 to 19.124	1.768 to 8.130
p	.001	.001	N/S	N/S

(Upper values : Rt. hand ; lower values : Lt. hand)
^ NCR : Not a clear response. N/S : not significant.

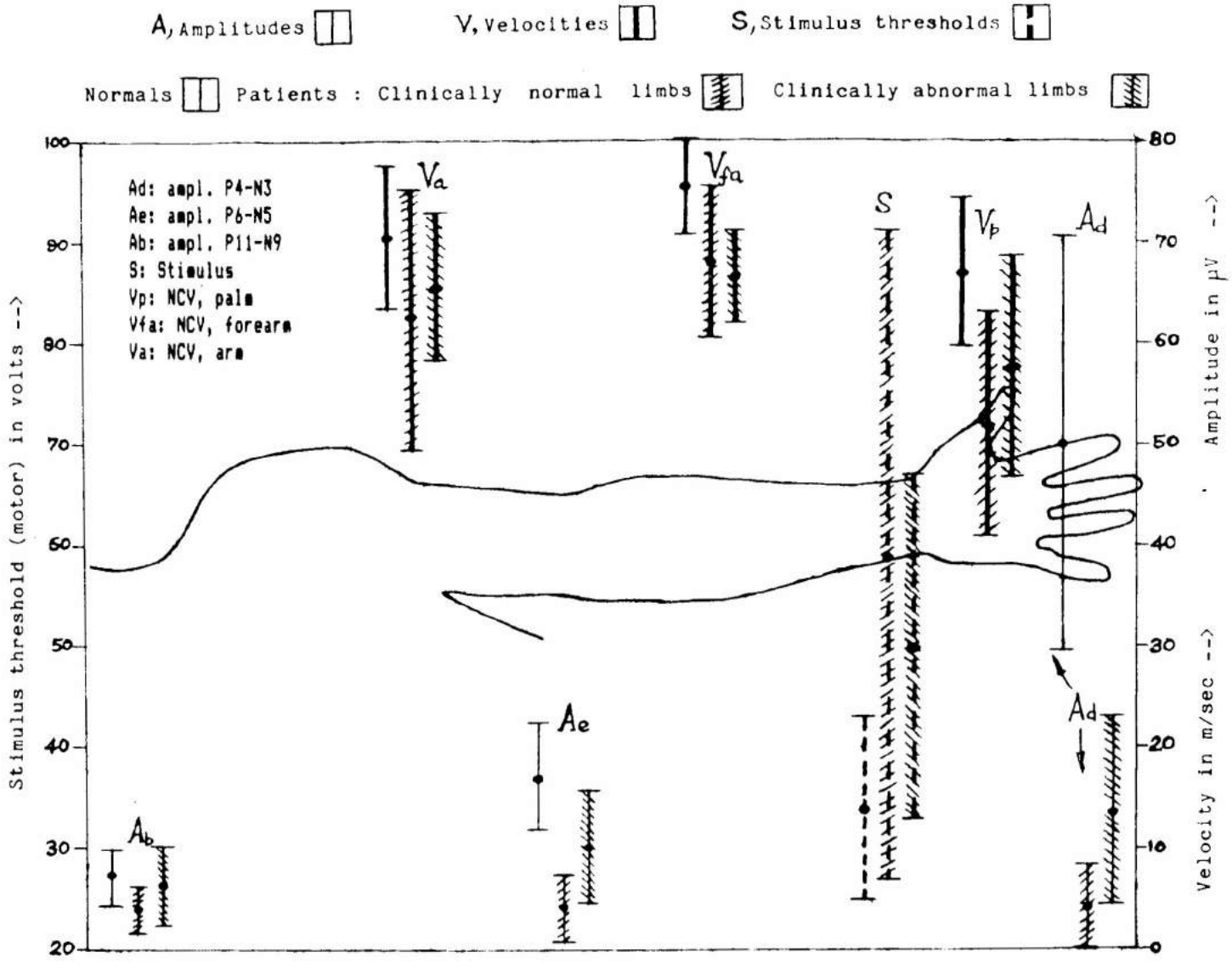


Fig.4.1 Mean (±S.D.) values of peripheral amplitudes, nerve conduction velocities and stimulus thresholds of both normals and leprosy patients.

5. MULTIVARIATE ANALYSIS AND SPECTRAL ANALYSIS

5.1 INTRODUCTION

In the previous chapter, the various parameters measured on the subjects and their sample statistics were presented. It is very inconvenient to deal with so many different variables, especially when there is an overlap in the range of values for normals and patients in some of the parameters. It will be ideal to obtain an integrated measure or index based on these parameters depending on the magnitude of which categorization of an individual as normal or abnormal will be possible.

Discriminant analysis is the appropriate statistical tool to use here [Tabachnick and Fidell, 1983] as this technique is normally used to classify an observation into one of two or more mutually exclusive and exhaustive groups on the basis of a set of predictor variables. In the present study, the interest lies mainly in classifying an individual into one of two distinct groups from the values of a set of numerical variables.

The approach in discriminant analysis is as follows. After dividing the sample into two or more groups, data is collected on the values of the variables for all the individuals belonging to each group. The discriminant analysis then derives a linear combination of these parameters which 'best' discriminates between these groups with least error. In the case of a dichotomy, the problem is to ascertain appropriate weights for a series of variables yielding maximum linear separation in the two contrasted groups (the assumption being that the distribution in

which the dichotomy exists is a single normally distributed variable [Kendall, 1980]).

5.1.1 Relevance of spectral analysis

The expectation of biological signal processing is that analysis may illuminate the signal content and that detailed sifting of a signal may lead to deductions about the source that generated the signal [Sayers, 1975]. Spectral analysis is a tool whose signal analysis applications appear in all branches of science and engineering. The speed of digital computer fast Fourier transform algorithms and the convenience of special-purpose instruments for correlation and spectral estimation have led to greatly increased use of these techniques in recent years. Presence or absence of energy in specific frequency bands can often be very informative. Such information has been used to study the development of brain dominance in man [Schwartz and Shaw, 1975]. Astrophysicists determine the presence of specific molecules in distant regions of space by the absorption or resonance spectra of those regions. In the present work, spectral analysis was undertaken in order to see whether there are any notable differences in the frequency domain between the normal and patient responses.

5.2 DISCRIMINANT ANALYSIS

The main objectives in pursuing discriminant analysis in the work reported here were : (i) To test whether significant differences exist between normals and patients, assuming the

distributions of the various parameters are multivariate normal. (ii) To determine which variables account most for such intergroup differences. (iii) To find a linear combination of the predictor variables that represents the two groups by maximizing the separation between the groups and minimizing the separation within the groups. (iv) To establish procedures for assigning new individuals to one of the groups, assuming that they come from one of the a priori defined groups (namely, normals and leprosy patients).

5.2.1 Principles

We consider the case of only two groups. We can fit a linear function of predictor variables $X_1, X_2, \ldots, X_p$ of the form

$$D = E_1 X_1 + E_2 X_2 + \ldots + E_p X_p \qquad \ldots [5.1]$$

where E's represent the discriminant coefficients and D is the value of the discriminant function (score) for a particular individual such that if this value is greater than a certain critical score D*, the individual would be classified in one group, otherwise in the other group. If we have n individuals measured on the p predictor variables and we also know the group to which each individual belongs (say, the first m individuals belong to the first group and remaining (n-m) individuals to the second group) then the data matrix would be $[X_{ij}]$, $i = 1,2,..,n$ and $j = 1,2,...,p$.

Let us denote the sample means of random variables $X_1, X_2, \ldots, X_p$ in group I by $\bar{X}_1^{(1)}, \bar{X}_2^{(1)}, \ldots, \bar{X}_p^{(1)}$ and that for group II by $\bar{X}_1^{(2)}, \bar{X}_2^{(2)}, \ldots, \bar{X}_p^{(2)}$ where

$$\bar{X}_j^{(1)} = 1/m \sum_{i=1}^{m} X_{ij} \text{ and } \bar{X}_j^{(2)} = 1 / (n-m) \sum_{i=m+1}^{n} X_{ij}$$

for j = 1,2,...,p. .... [5.2]

Define $S_{ij}^{(1)} = \sum_{k=1}^{m} (X_{ki} - \bar{X}_i^{(1)}) (X_{kj} - \bar{X}_j^{(1)})$ .... [5.3]

and let the matrix of sum of squares and products for group I be

$S^{(1)} = [S_{ij}^{(1)}]$. Similarly, define

$$S_{ij}^{(2)} = \sum_{k=m+1}^{n} (X_{ki} - \bar{X}_i^{(2)}) (X_{kj} - \bar{X}_j^{(2)}) \quad \text{.... [5.4]}$$

and the matrix of sum of squares and products for group II be

$S^{(2)} = [S_{ij}^{(2)}]$.

Then, the estimate of population variances and covariances of the predictor variables is given by the matrix

$$S = (S^{(1)} + S^{(2)}) / (n-2) = [S_{ij}] \quad \text{.... [5.5]}$$

Finally, the distance between the sample means of the two groups for the ith predictor variable, d_i is

$$d_i = \bar{X}_i^{(1)} - \bar{X}_i^{(2)}, \; i = 1,2,..,p \quad \text{.... [5.6]}$$

The ultimate aim is to choose a set of E's from the set of all possible E's such that the average score for group I be as far away as possible from the average score for group II. That is, we have to choose the E's in such a way that they maximize the distance $(\bar{D}1 - \bar{D}2)$ relative to the dispersion of the respective scores, where $\bar{D}1$ and $\bar{D}2$ are the mean scores of groups I and II respectively which are algebraically given by

$$\bar{D}1 = E_1 \bar{X}_1^{(1)} + E_2 \bar{X}_2^{(1)} + \ldots + E_p \bar{X}_p^{(1)} \quad \text{.... [5.7]}$$

and $$\bar{D}2 = E_1 \bar{X}_1^{(2)} + E_2 \bar{X}_2^{(2)} + \ldots + E_p \bar{X}_p^{(2)} \quad \text{.... [5.8]}$$

This can be achieved by choosing E's so as to maximize

$$G = \frac{(\bar{D}1 - \bar{D}2)^2}{\sum_{i=1}^{m} (D_{1j} - \bar{D}1)^2 + \sum_{j=m+1}^{n} (D_{2j} - \bar{D}2)^2} \quad \text{.... [5.9]}$$

where $D_{ij} = \sum_{k=1}^{p} E_k X_{jk}$ for i = 1, j = 1,2, ... , m

i = 2, j = m+1,m+2,..,n.

That is, the technique estimates the E's which maximize the ratio of the squared difference between the group means to the variance within the groups.

It can be shown that G will be maximum when E's are given by

$$[E] = S^{-1} [D], \quad \ldots. [5.10]$$

where [E] is a column vector of the coefficients and D is a column vector of the distances d_j between the sample means of the two groups for the p variables. The values of $\overline{D1}$ and $\overline{D2}$ are made use of for identifying whether a new individual (with a set of values x_1 to x_p) belongs to group I or II depending upon the closeness of the new score to $\overline{D1}$ or $\overline{D2}$. Specifically, we can choose D*, a critical score, lying between $\overline{D1}$ and $\overline{D2}$, such that if the new score lies on the same side of D* as $\overline{D1}$, then the individual belongs to group I, otherwise, the individual belongs to group II. Usually, D* is taken to be $(\overline{D1} + \overline{D2}) / 2$.

The particular simple form of linear discriminant function allows a clear interpretation of the effect of each of the predictor variables. The discriminating power of each variable is expressed as a percentage of the Mahalanobis' generalised distance, D^2, between the two groups. The latter(D^2)is defined as

$$D^2 = \sum_{i=1}^{p} E_i d_i. \quad \ldots. [5.11]$$

The power, C_i of any predictor variable Xi is then given by

$$C_i = (Ei * d_i) / D^2 * 100. \quad \ldots. [5.12]$$

$$\text{The test statistic } F = \frac{n-p-1}{p} * \frac{m\,(n-m)}{n\,(n-2)}\, D^2 \qquad \ldots\ldots [5.13]$$

is used for testing the significance of differences between mean values of two multivariate normal populations with the same dispersion matrix and the test statistic is distributed as F-distribution with p and (n-p-1) degrees of freedom.

5.2.2 Results and discussion

If the analysis uses data on n observations to calculate the discriminant function and then classifies the same n observations, then the results will be biased. There will be more correct classifications than the discriminant function is capable of delivering under more realistic conditions. To avoid this, it is advisable to fit a function to part of the data and then use this function to classify the remaining individuals. Hence, of the 25 normal data collected, 18 were used to determine the discriminant function, reserving the rest to test the efficacy of the obtained classifier. To have a clear demarcation between the normal and patient data, only the data from the clinically (median nerve) affected upper limbs were employed in arriving at the discriminant function. Thus, of the 42 sets of upper limb responses from 21 patients, only 17 were included in the procedure for estimation of the coefficients of the linear discriminant function. To begin with, 13 parameters were considered, namely, the stimulus threshold, the four fall times, the central conduction time, the three segmental nerve conduction velocities and the four peak to peak amplitudes of the responses.

Table 5.1 lists the values of the discriminant coefficients determined by this technique. Since the range of values of the fall times is considerably smaller than the range of values of the other variables considered in the analysis, the true significance of each predictor variable can be discerned only by seeing its relative contribution to the separation between the mean scores of the two groups. Towards this purpose, Table 5.1 also lists the product of each coefficient Ei with the distance di between the sample means of the two groups for the corresponding predictor variable. The fourth column gives the discriminating power of each variable which is the above mentioned product (Ei*di) expressed as the percentage of the Mahalanobis' distance between the two groups. Table 5.2 shows the value of the discriminant function for each of the data and the resultant classification. A '*' in the table preceding the subject ID No. identifies those data which were utilized to determine the discriminant function. The F value of 15.65, obtained using eqn. [5.13] is very high compared to the table value of F distribution (13,21 degrees of freedom) at .05% level($p<.0005$) denoting that the 2 groups are very significantly distinct. It also means that the classifier is highly effective in discriminating between the two groups. The discriminant function is able to classify all the 25 normal data as belonging to group 1, namely normal. The classifier also classifies 38 out of the 42 responses from patients as abnormal. It is interesting to see that the discriminant classifier is able to pick up 4 sets of responses obtained from the unaffected upper limbs of the

patients as normal (the underlined data in Table 5.2). Another point to note is that of the 25 sets of responses excluded while determining the classifier on the basis that there were no clinical abnormality of the median nerve, as many as 21 sets have been classified as abnormal by the classifier.

An inspection of Table 5.1 shows that the discriminating power of each of the parameters 2,3,4,5,6,9,12 and 13 is less than 8%, while that of the others is >= 15%. So, a second run of the analysis was performed after eliminating the former (less significant) variables. Tables 5.3 and 5.4 give the results of the analysis using the remaining 5 predictor variables. Interestingly, this function with only 5 parameters is almost as effective ($p<.0005$) as the first classifier with 13 parameters in that it has rightly classified all the normals and the clinically affected patient limbs and thus the percentage of correct classification is 100 for these sets of data. Again, 4 of the remaining 25 sets of data from clinically normal limbs are classified as normals, while the other 21 sets of responses from limbs with clinically confirmed **involvement of only ulnar nerve** are declared abnormal with respect to the median nerve also. All the 5 predictor variables have a good discriminating power, contributing 10% to 30% to the mean separation between the groups. This result quantitatively confirms the conclusion reached on the basis of the time domain analysis that the two distal responses sufficiently identify an abnormal median nerve.

However, from the point of view of a field survey, it will be ideal if classification (as normal or abnormal) is possible

based on the response obtained from a single recording site. Hence, in the next iteration, the effectiveness of a classifier involving only 3 parameters was studied. These are the digital response amplitude,Ad, palm segmental conduction velocity,Vp and the stimulus strength,S. The discriminant coefficients obtained in this third iteration and the consequent classification of data are tabulated in Tables 5.5 and 5.6 respectively. The intergroup separation based on only these 3 variables is again very highly significant ($p<.0005$). The false negative classification of the control subject N7 is due to the unusually high threshold of 57 volts. This value might have resulted from improper positioning of the stimulating electrodes with respect to the nerve and/or improper cleaning of the stimulus site. Let us consider each of the 4 sets of data (see Table 5.6) from patient limbs classified as normal. In the case of the patient P5, the stimulus threshold is very low, since he is a young boy (age 15, lower than the control group). Also, his right hand is normal with normal values of NCVs and amplitudes and with no clinical symptoms. Hence the classification of P5-R as normal is justified. Patient P13, as already discussed in chapter 4, has been fully cured of the disease and thus is rightly classified. Lastly, the patient P20 too has a perfectly normal right hand, both by the absence of symptoms and by the values of the various variables. Now, looking at the clinically normal data classified as abnormal, P4, for example, has ulnar nerve involvement in both hands and median nerve involvement in right hand only. The left arm digit potential has a very low amplitude of 2.009 μV (see Table 4.8),

suggesting severe neuropathy of the left median nerve. The NCV of the distal segment(palm) too has a very low value of 35.2 m/sec. The classifier, though trained with data from clinically abnormal nerves, is able to correctly classify affected nerves as this, which, however, show no clinical dysfunction. This shows the efficacy of the classifier and also proves that electrophysiological studies can reveal neural abnormalities earlier to the clinical manifestation of the disease.

Thus the 3-predictor classifier is found to be capable of identifying both normal and abnormal hands of patients properly. The false negative classification can be avoided by biasing the critical score value. This, however, may entail a few false positive classifications and thus may work contrary to interest. However, 24 out of 25 normals(96%) have been rightly classified, thus proving the usefulness of the discriminant function.

5.3 SPECTRAL ANALYSIS

The absolute and relative power spectra of the compound nerve action potentials and the cortical evoked potentials were computed using a bell shaped window and fast Fourier transform [Brigham, 1974]. Since the response at each recording site was obtained twice, the average of the spectra of the two trials was computed and taken as the spectrum for a particular response. The spectra of patients were studied in comparison with those of normals. The power spectra of the responses from a normal subject and a patient are shown in Figs. 5.1 to 5.4. The power spectra of the distal peripheral potentials (from digit and elbow) for

normals are very smooth with no noticeable peaks, whereas notable clear peaks are present at frequencies around 1000 and 1500 Hz in the spectra of both the potentials of patients. In the case of the brachial plexus response(Erb's point), a peak occurs around 1500 Hz in both types of subjects, but the peak is much sharper in patients. Again in Hansen's disease patients, another peak around 2525 Hz appears in the spectra of the centrally evoked potentials in addition to the one around 1500 Hz, the latter being common in normal subjects as well. To confirm that there is a common trend among the responses of all the patients and that there is a different trend among the normal responses, average spectra were obtained from the 18 sets of normal data and the 17 sets of patient data. The Fig. 5.5 compares the average spectra of the normal and leprosy subjects. These average spectra confirm the existence of the above mentioned peaks. There is practically no difference between the normal and patient responses with reference to the cortical potentials except for the peak around 2525 Hz.

To exclude the possibility that the peaks might be due to some inherent characteristics of the recording system, check responses were obtained by similar averaging, with the same parameters like stimulus repetition frequency, etc., twice, once with the amplifier inputs shorted and once again with the inputs open. Such mock responses were obtained with the averaging parameters corresponding to all the four recording sites. Further, this procedure was conducted both at the laboratory where the normal subjects were studied and at the Central Leprosy

Research and Teaching Institute where the patients were studied. Since there is automatic gain control in the input amplifier, even the short circuit responses are brought to a level close to the input range of the analog to digital converter and thus the integrity of the frequency contents of these open and short circuit responses are well maintained. Spectra of these test responses do not exhibit any of the peaks noticed in the case of either the normals or leprosy patients. Again the average of the spectra of the four check responses (open and short circuit responses at the two geographical locations) were computed. Fig 5.6 shows the average spectra of these check data and there are no appreciable peaks in the frequencies at which the neural responses have discernible peaks. This confirms that the amplifier or other system characteristics have not been responsible for the specific spectral patterns. Thus the peaks observed in the frequency domain are due to sources which are electrophysiological in origin, though the exact nature of these origins is not clear at this stage.

5.4 CONCLUSIONS

The discriminant analysis confirms that the compound nerve action potentials recorded from the median nerve at the elbow and third digit show discernable abnormalities much earlier to the clinical manifestation in the form of sensory or motor deficit. The results clearly show that a classifier with only three variables is fully capable of distinguishing between normal and abnormal median nerve responses. This discriminant function is given by,

$$D = -0.063\ S + 0.1817\ V_p + 0.2081\ A_d,$$

where S is the motor threshold of stimulation ,

V_p is the NCV of the palm segment,

and A_d is the amplitude of the digit potential.

Thus, in a field situation, for a preliminary screening of the exposed population, it suffices to take only the digit response to median nerve stimulation at the wrist and to note the stimulus threshold. A quick decision can be taken and the whole testing and estimation procedure will take only 15 minutes.

However, it is felt that a waveshape analysis might provide additional information leading to a better criterion for discriminating normal from abnormal responses and this analysis is reported in chapter 6.

The spectra of the normal and patient responses display certain characteristic peaks in specific frequencies. This fact has not been reported so far and hence provides a new insight into electrophysiological changes in leprosy. In patients, the increased peak around 1.5 KHz is seen only upto Erb's point and not centrally - where the powers for normals and patients are identical. The origins of this spectral behaviour are not yet known. There may be preferential axonal degeneration or a changed impedance of axons due to the degeneration of myelin sheath producing an impedance mismatch and a resonance at 1.5 KHz. However, this is only a conjecture and needs to be addressed more fully through extensive investigations.

TABLE 5.1 SIGNIFICANCE OF THE PREDICTORS
(No. of var. = 13)

PAR. No.	PARA METER	COEFF. Ei	di= $\bar{X}i(1) - \bar{X}i(2)$	SEPARATION Ei * di	D.POWER % of D^2
1	STIMULUS	-0.2821	-25	7.0032	19.7
2	P4-N3,msec	9.4311	0.21	1.9531	5.5
3	P6-N5,msec	-1.1583	-0.14	0.1636	0.5
4	P11-N9,msec	2.1410	-0.21	-0.4404	-1.2
5	P22-N19,msec	-0.4941	0.93	-0.4597	-1.3
6	CCT,msec	-0.2717	-0.06	0.0148	0.0
7	Vp,m/sec	0.3981	15.0	5.9723	16.8
8	Vfa,m/sec	0.8022	6.5	5.2178	14.7
9	Va,m/sec	-0.2677	8.9	-2.3857	-6.7
10	Ad,uV	0.2208	48.30	10.6655	30.1
11	Ae,uV	0.8374	13.11	10.9806	31.0
12	Ab,uV	-0.8113	3.43	-2.7824	-7.8
13	As,uV	-0.6961	0.63	-0.4375	-1.2

TABLE 5.2 CLASSIFICATION OF DATA BY THE DISCRIMINANT FUNCTION OF 13 VARIABLES

($\bar{D}1$ = 82.7358 $\bar{D}2$ = 47.2706 D* = 65.0032)

SUBJ	D	GROUP	SUBJ	D	GROUP	SUBJ	D	GR.
N1	70.10	1^	*N24	92.68	1^	P11R	30.15	2
N2	66.05	1	*N25	83.29	1	P11L	42.89	2
*N3	92.45	1	P 1R	63.42	2	*P12R	49.28	2
*N4	91.53	1	P 1L	70.23	1	*P12L	51.50	2
*N5	77.64	1	*P 2R	47.08	2	P13R	74.18	1
*N7	71.26	1	P 2L	64.35	2	P13L	64.02	2
*N8	78.43	1	*P 3R	42.61	2	*P14R	51.98	2
*N9	71.76	1	*P 3L	52.40	2	P14L	58.57	2
*N10	86.12	1	P 4R	0.53	2	P15R	66.64	1
N11	80.90	1	P 4L	37.20	2	P15L	49.33	2
N12	96.86	1	P 5R	60.72	2	P16R	44.60	2
*N13	85.90	1	*P 5L	46.71	2	P16L	55.58	2
*N14	75.63	1	*P 6R	43.71	2	P17R	46.56	2
*N15	73.06	1	P 6L	52.98	2	P17L	64.72	2
*N16	78.29	1	P 7R	38.30	2	*P18R	50.78	2
N17	93.06	1	*P 7L	41.53	2	*P18L	51.09	2
N18	65.86	1	*P 8R	47.30	2	P19R	-4.61	2
*N19	87.09	1	*P 8L	39.02	2	P19L	50.73	2
*N20	87.38	1	P 9R	58.34	2	P20R	69.11	1
*N21	89.36	1	*P 9L	55.56	2	*P20L	42.82	2
*N22	84.16	1	*P10R	45.23	2	P21R	61.06	2
N23	105.20	1	*P10L	45.01	2	P21L	56.05	2

^ 1 : Normal 2 : Abnormal
* data utilized in arriving at the discriminant coeffs.

TABLE 5.3 SIGNIFICANCE OF PREDICTORS
(No. of var. = 5)

PAR No.	PARA METER	COEFF. Ei	SEPARATION Ei * di	DISC. POWER % of D^2
1	STIM.	-0.1726	4.2839	15.1762
2	Vp	0.1935	2.9037	10.2867
3	Vfa	0.6513	4.2361	15.0071
4	Ad	0.1803	8.7094	30.8541
5	Ae	0.6173	8.0945	28.6759

TABLE 5.4 CLASSIFICATION OF DATA BY THE DISCRIMINANT FUNCTION OF 5 VARIABLES

($\overline{D1}$ = 75.8712 $\overline{D2}$ = 47.6436 D* = 61.7574)

SUBJ ID	D	GROUP	SUBJ ID	D	GROUP	SUBJ ID	D	GR.
N 1	63.349	1^	P 1R	57.601	2^	P13L	62.146	1
N 2	62.043	1	P 1L	67.236	1	*P14R	52.356	2
*N 3	81.886	1	*P 2R	48.086	2	P14L	58.269	2
*N 4	86.233	1	P 2L	57.017	2	P15R	60.755	2
*N 5	68.536	1	*P 3R	44.710	2	P15L	50.584	2
*N 6	77.045	1	*P 3L	52.414	2	P16R	45.976	2
*N 7	64.137	1	P 4R	28.656	2	P16L	46.819	2
*N 8	70.543	1	P 4L	40.459	2	P17R	48.544	2
*N 9	69.442	1	P 5R	65.454	1	P17L	57.611	2
*N10	77.268	1	*P 5L	49.575	2	*P18R	52.389	2
N11	72.597	1	*P 6R	45.437	2	*P18L	49.336	2
N12	83.767	1	P 6L	53.970	2	P19R	21.137	2
*N13	82.037	1	P 7R	41.855	2	P19L	33.880	2
*N14	71.684	1	*P 7L	41.940	2	P20R	59.569	2
*N15	70.835	1	*P 8R	43.309	2	*P20L	43.174	2
*N16	71.646	1	*P 8L	43.981	2	P21R	56.294	2
N17	78.894	1	P 9R	59.945	2	P21L	56.470	2
N18	65.477	1	*P 9L	55.113	2			
*N19	79.219	1	*P10R	40.261	2			
*N20	79.140	1	*P10L	47.066	2			
*N21	80.898	1	P11R	41.280	2			
*N22	76.536	1	P11L	42.507	2			
N23	87.705	1	*P12R	54.163	2			
*N24	82.967	1	*P12L	46.633	2			
*N25	75.630	1	P13R	71.659	1			

^ 1 : Normal 2 : Abnormal
* data utilized in arriving at the discriminant coeffs.

TABLE 5.5 SIGNIFICANCE OF PREDICTORS
(No. of var. = 3)

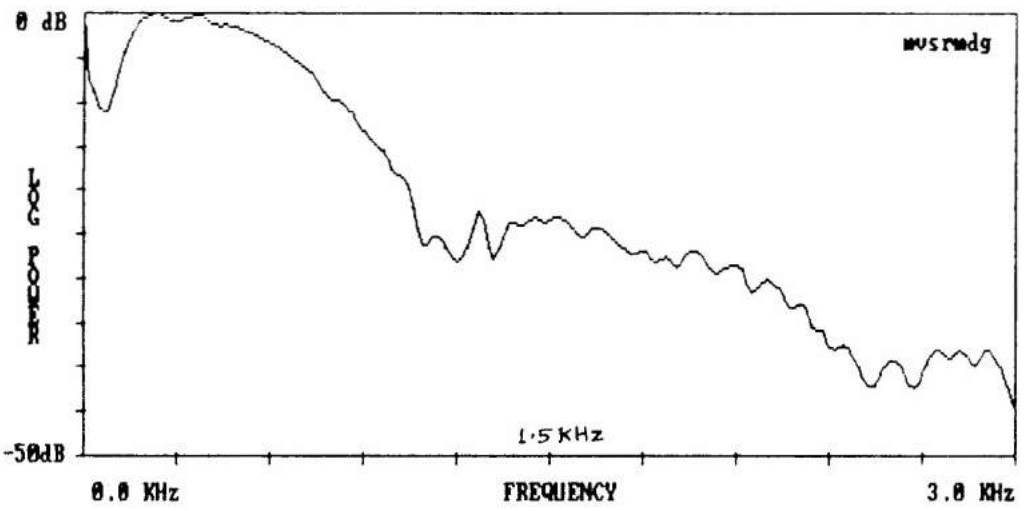
PARA METER	COEFF. Ei	SEPARATION Ei * di	DISC. POWER % of D^2
STIM.	-0.0630	1.5639	10.9040
Vp	0.1817	2.7262	19.0084
Ad	0.2081	10.0520	70.0876

TABLE 5.6 CLASSIFICATION OF DATA BY THE DISCRIMINANT FUNCTION OF 3 VARIABLES

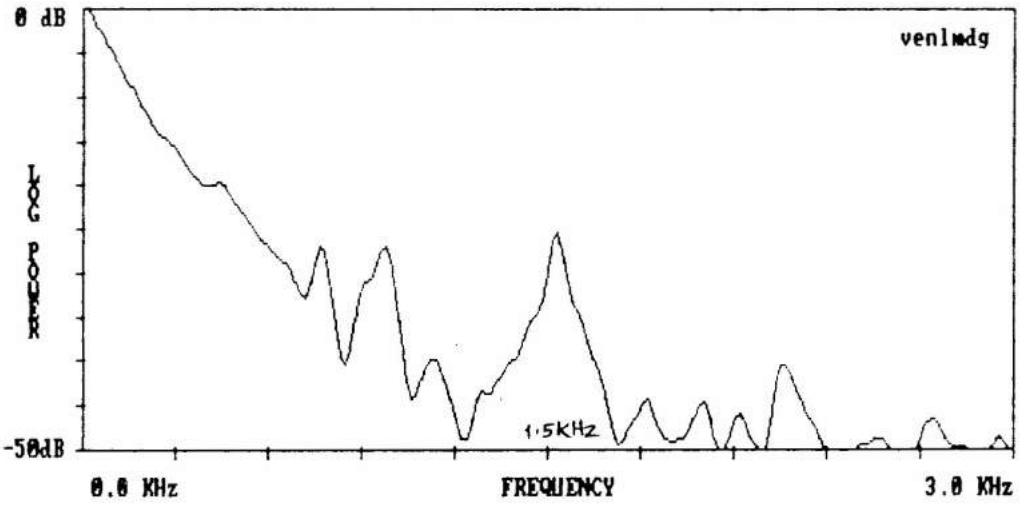
($\overline{D1}$ = 20.9726 $\overline{D2}$ = 6.6306 D* = 13.8016)

SUBJ ID	D	GROUP	SUBJ ID	D	GROUP	SUBJ ID	D	GR.
N 1	15.067	1^	P 1R	11.282	2^	P13L	14.069	1
N 2	14.117	1	P 1L	12.853	2	*P14R	10.324	2
*N 3	28.373	1	*P 2R	7.143	2	P14L	13.288	2
*N 4	24.649	1	P 2L	9.688	2	P15R	12.689	2
*N 5	18.049	1	*P 3R	10.062	2	P15L	11.238	2
*N 6	18.599	1	*P 3L	6.911	2	P16R	6.564	2
*N 7	12.064	2	P 4R	-7.244	2	P16L	7.190	2
*N 8	16.879	1	P 4L	2.027	2	P17R	7.900	2
*N 9	19.977	1	P 5R	14.241	1	P17L	11.899	2
*N10	20.370	1	*P 5L	3.748	2	*P18R	11.331	2
N11	21.205	1	*P 6R	3.625	2	*P18L	7.726	2
N12	16.738	1	P 6L	12.644	2	P19R	-5.417	2
*N13	29.614	1	P 7R	4.495	2	P19L	-6.425	2
*N14	17.784	1	*P 7L	5.108	2	P20R	14.098	1
*N15	19.093	1	*P 8R	7.666	2	*P20L	0.781	2
*N16	20.758	1	*P 8L	5.421	2	P21R	9.403	2
N17	21.229	1	P 9R	12.444	2	P21L	8.743	2
N18	14.378	1	*P 9L	8.090	2			
*N19	17.661	1	*P10R	4.724	2			
*N20	22.470	1	*P10L	8.515	2			
*N21	24.902	1	P11R	6.488	2			
*N22	22.072	1	P11L	5.172	2			
N23	25.600	1	*P12R	8.242	2			
*N24	26.792	1	*P12L	3.304	2			
*N25	17.401	1	P13R	15.437	1			

^ 1 : Normal 2 : Abnormal
* data utilized in arriving at the discriminant coeffs.

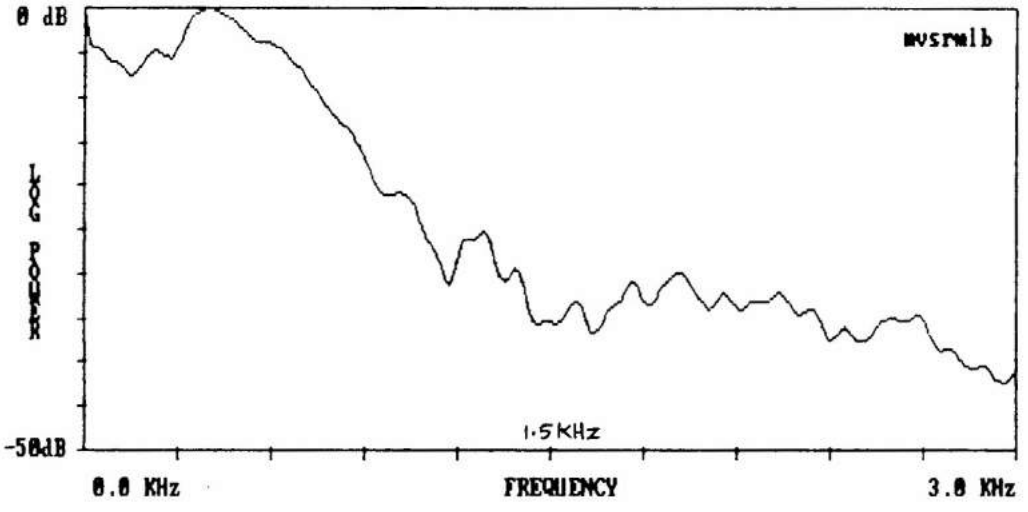


5.1.a. Spectrum of a normal response

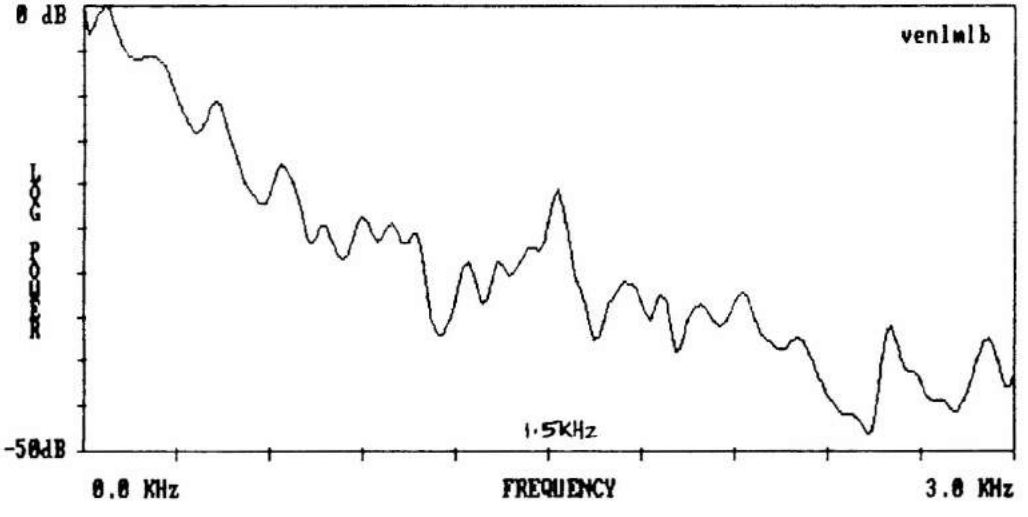


5.1.b. Spectrum of a patient response

Fig.5.1. Power spectra of compound nerve action potentials recorded from the third digit.

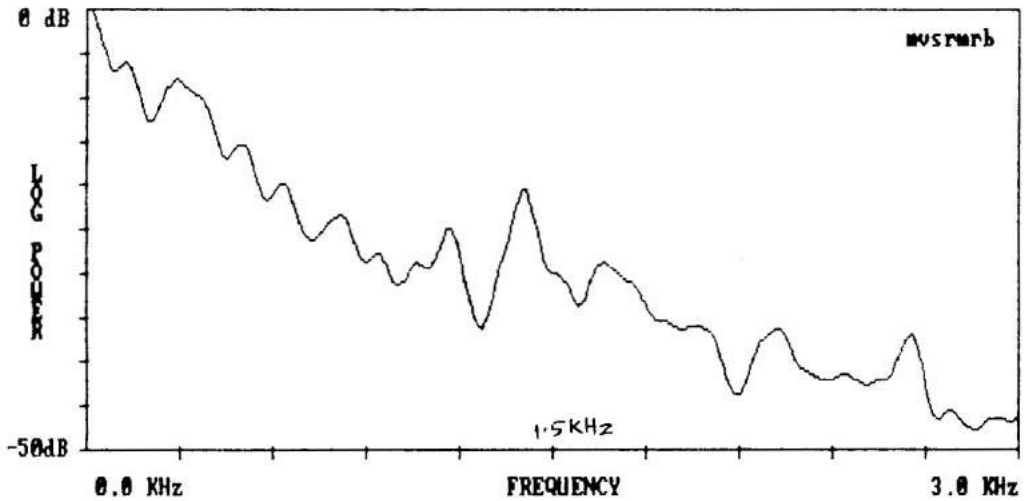


5.2.a. Spectrum of a normal response

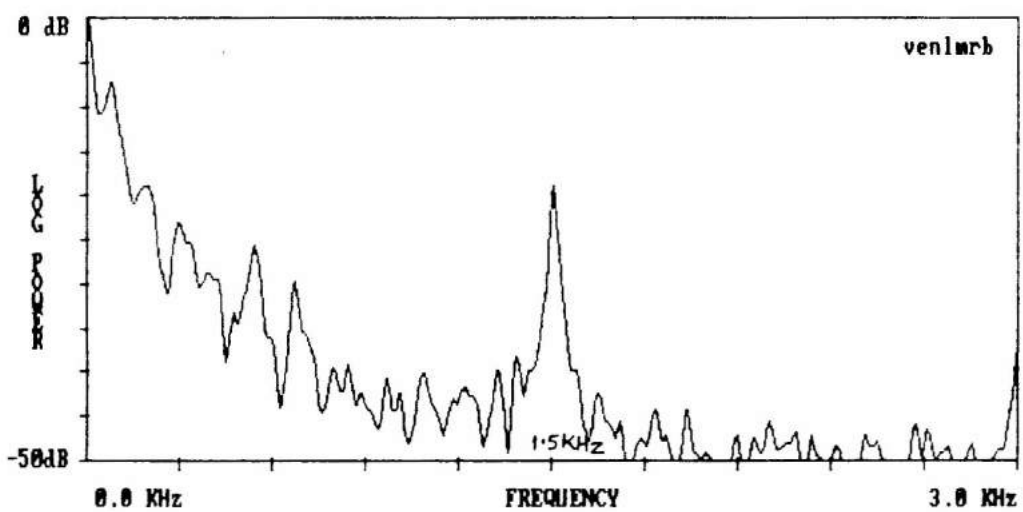


5.2.b. Spectrum of a patient response

Fig.5.2. Power spectra of compound nerve action potentials recorded from the elbow.

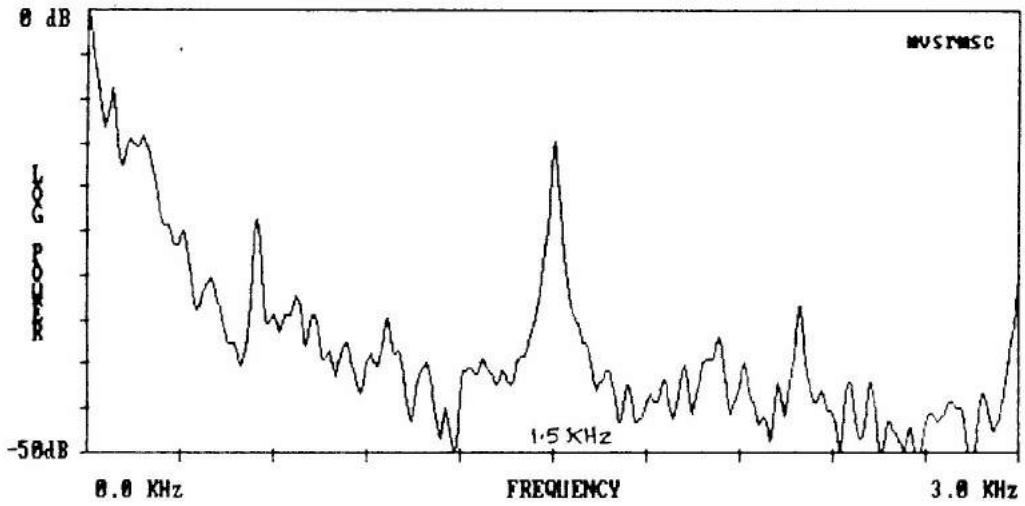


5.3.a. Spectrum of a normal response

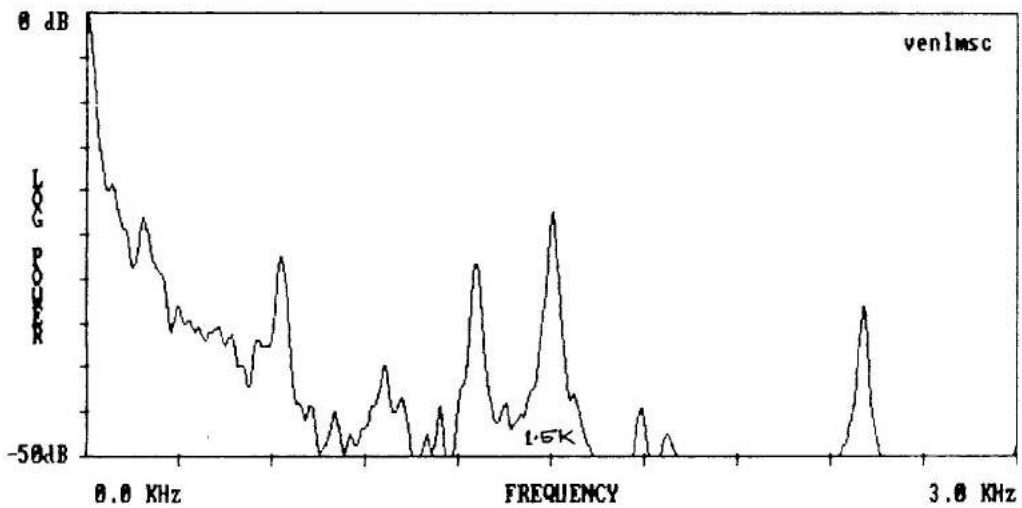


5.3.b. Spectrum of a patient response

Fig.5.3. Power spectra of evoked potentials recorded from the Erb's point.

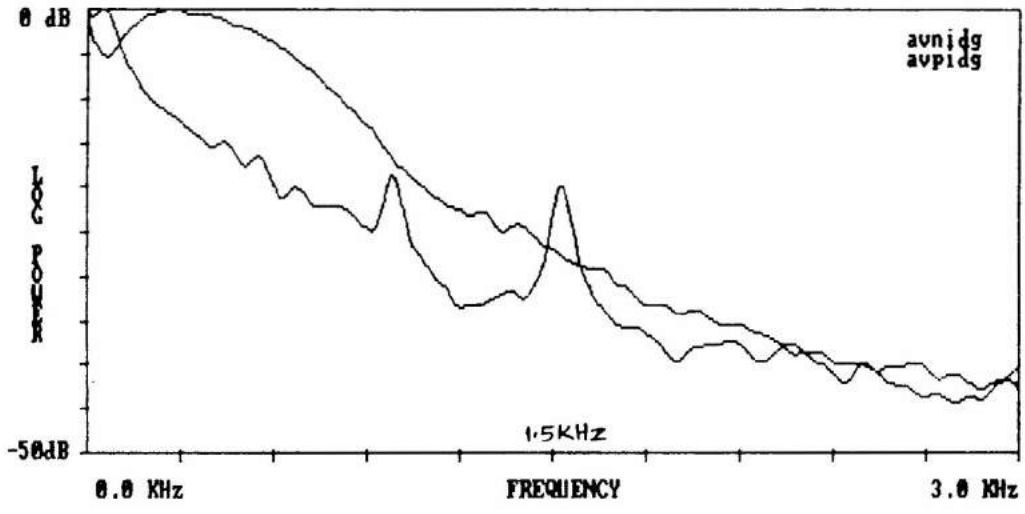


5.4.a. Spectrum of a normal response

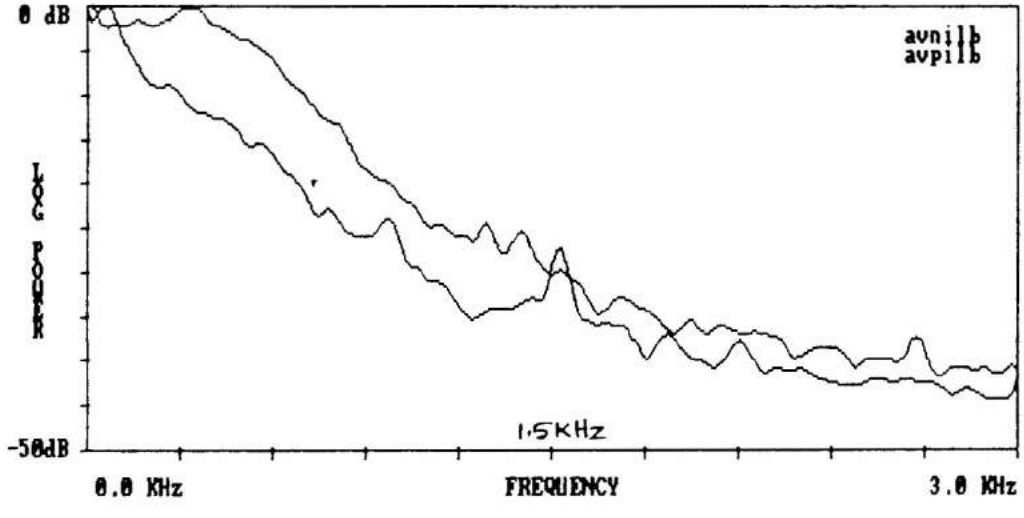


5.4.b. Spectrum of a patient response

Fig.5.4. Power spectra of somatosensory evoked potentials recorded from the contralateral cortex.

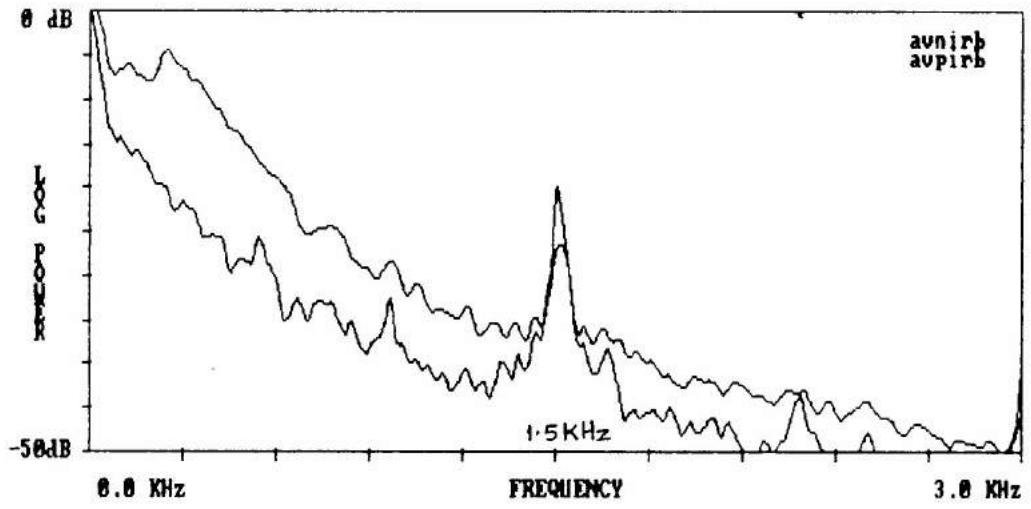


5.5.a Spectra of digit responses

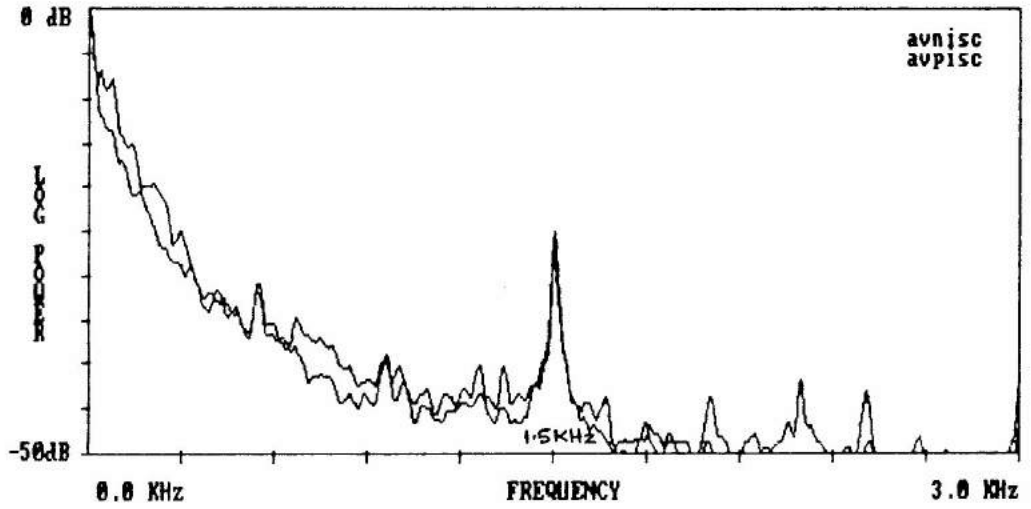


5.5.b Spectra of elbow responses

Fig.5.5 Comparison of the average spectra of normal and patient responses.

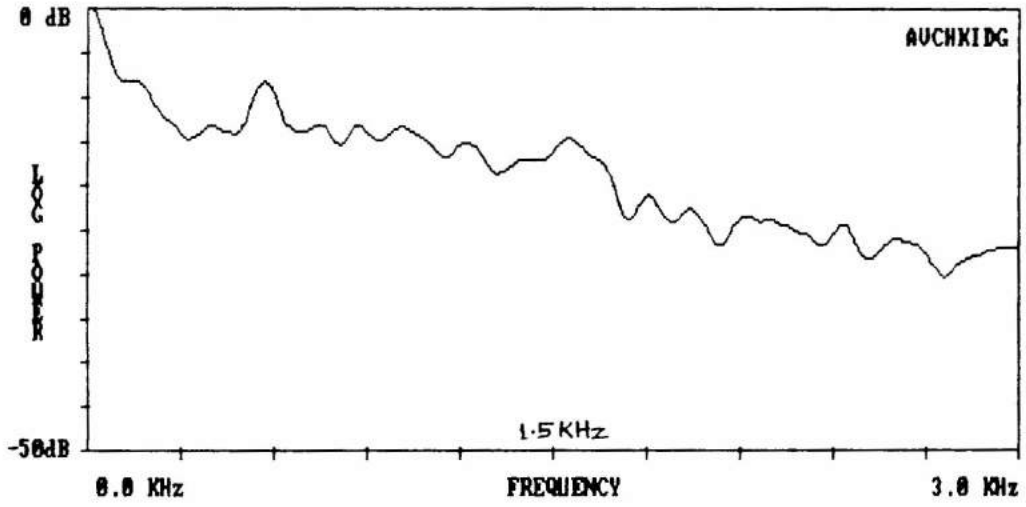


5.5.c Spectra of Erb's point responses

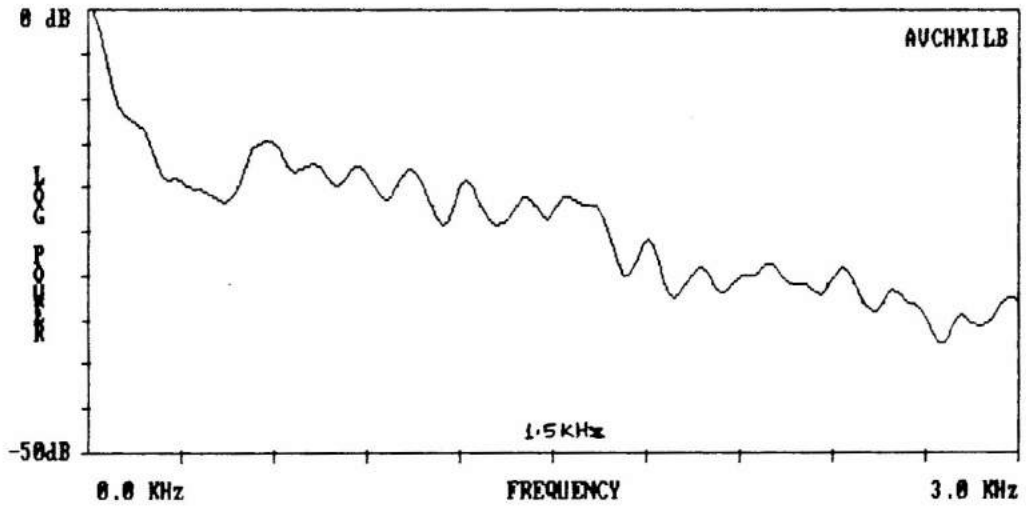


5.5.d Spectra of cortical SEPs

Fig.5.5 Comparison of the average spectra of normal and patient responses - contd.

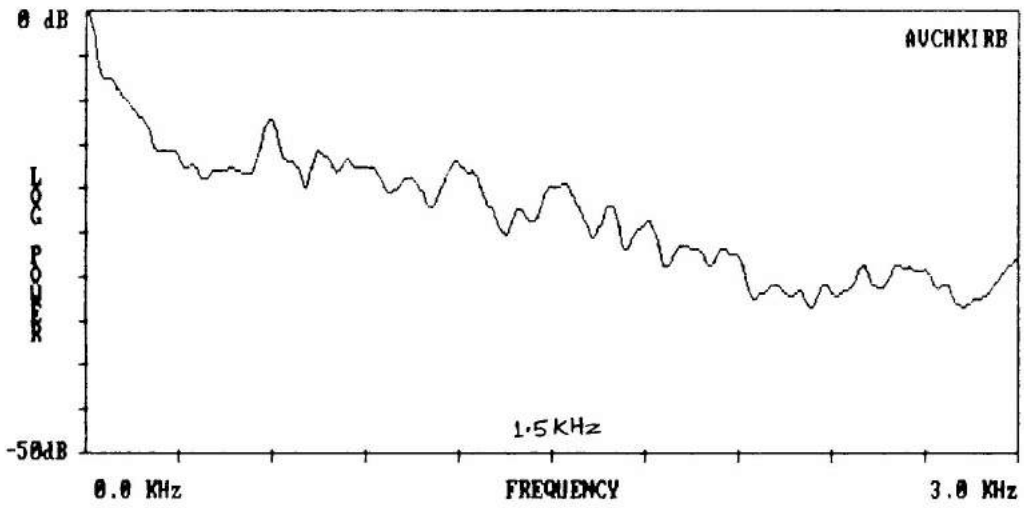


5.6.a. Recording parameters same as that for digital responses

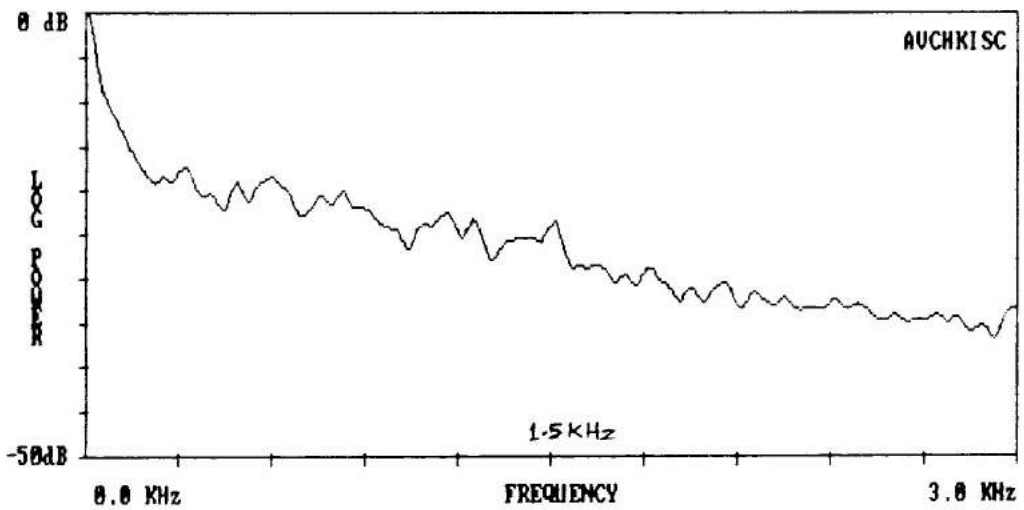


5.6.b. Recording parameters same as that for elbow responses

Fig.5.6. Average spectra of test responses obtained for examining system induced frequency characteristics.



5.6.c. Recording parameters same as that for brachial plexus responses



5.6.d. Recording parameters same as that for cortical responses

Fig.5.6. Average spectra of test responses obtained for examining system induced frequency characteristics-contd.

6. CLASSIFICATION OF EP DATA BY TREE MATCHING

6.1 INTRODUCTION

Chapters 4 and 5 dealt chiefly with the amplitude and time of occurrence of the major response peaks. A visual inspection of the normal and abnormal responses suggested an analysis which will study and quantify the distortion in the waveshape and presence of additional, spurious peaks in the patient responses. So, both the normal and patient waveforms were represented by a tree structure known as a skeletal tree [Parthasarathy et al., 1986]. A reference waveform was obtained as the average of several normal responses. All the waveform trees were matched to this reference tree and a measure of the error of each waveform with respect to the reference was obtained. This method is also able to identify the number of peaks (genuine as well as pathological) in each response as equal to the number of leaf nodes in the corresponding tree.

6.2 SKELETAL TREE REPRESENTATION

The idea of representing waveforms by trees was first proposed by Ehrich and Foith[1976]. Tree representation is a two dimensional description language. Its application to waveforms provides not only a linear description of the succession of peaks and valleys on a waveform, but also a description of the self-embedding structure of a waveform. A peak on a waveform is itself a waveform that contains a series of smaller peaks and valleys. In a tree representation then, a node on a tree is itself a root of a subtree. Here, a scheme for representing waveforms by rooted

and directed trees [Cheng and Lu, 1985] is described.

6.2.1 Principles

First the amplitude range of the waveform is divided into a fixed number of quantization levels. Each pair of crossings enclosed by the waveform on a quantization level delineates an interval. For the first quantization level, the interval is the entire waveform. A node is created for this interval and is designated as the root of the tree. From the interval corresponding to the current node to intervals on the next quantization level above, tree nodes are created for these intervals and assigned as the son nodes of the current node. This recursive procedure continues until no further crossings can be found. The algorithm for the construction of a skeletal tree for a waveform with **ydiv** quantization levels is described as follows. The input to the algorithm is a waveform y(t) :

$$y(t) = \begin{cases} 0, \text{ if } t = 1 \text{ or } \mathbf{smpls} \\ 0 < y(t) <= \text{ydiv} * \mathbf{yscl}, \text{ if } 1 < t < \text{smpls} \end{cases} \quad \ldots\ldots [6.1]$$

where **smpls** is the maximum value of the time coordinate of the waveform and **yscl** is the amplitude of each quantization level. The output of the algorithm is a skeletal tree, T. **n**(tbegin,tend) denotes a tree node that has time domain from tbegin to tend. **ylim** is the current quantization level.

The algorithm proceeds as follows :

Let n(1,smpls) be the root node of the tree T.

Set ylim = yscl.

Call subtree (n(1,smpls), ylim).

Stop.

Subroutine subtree (n(tb,te), ylim) :

i] ylim = ylim + yscl.

ii] Find p_1, p_2, ... ,p_m such that tb < p_1 < p_2 < ... < te, and $y(p_j)$ = ylim for j = 1, 2, ... , m.

iii] If no such p's can be found, return. Else do step iv.

iv] For j = 1, 2, ... , m/2

Let node $n(p_{j*2-1},p_{j*2})$ be the jth son of the node n(tb,te).

Call subtree ($n(p_{j*2-1},p_{j*2})$, ylim).

During the implementation of this algorithm, several problems arise. Flat line segments of the waveform erroneously increase the number of cutting points m and thus introduce invalid (zero) intervals. Again, when the bottom of a valley coincides with an amplitude quantization level, the number of crossings is increased by one only instead of by two. Further, the number of crossings becomes an odd number due to the peculiarities of individual potentials and/or the effect of the quantization levels. The program was designed to take care of such situations. Also, the waveforms were first operated upon by a suitable bell shaped window to remove the stimulus artifact, if any.

6.2.2 Effect of quantization levels

Fig. 6.1 shows the skeletal tree of the Erb's point potential from a normal subject. Here, 15 quantization levels are

used. From the figure, the following properties of the skeletal tree representation are observed : The depth of a tree is equal to the number of quantization levels. The leaves of a tree are a linear description of the peaks in the waveforms, except that small peaks under the resolution of quantization are missed. The depth of a leaf is equal to the amplitude of the corresponding peak on the waveform. The nearest common predecessor of two nodes corresponds to a valley on the waveform.

Fig. 6.2 shows the skeletal tree of a patient waveform using 15 quantization levels. The distortion of the waveform as well as its spread out nature have been clearly brought out by the representation. Fig. 6.3 shows the tree of the same waveform with the number of quantization levels doubled. It is seen that the number of nodes has increased considerably though the information content of the tree has not improved appreciably. On the other hand, too few a number of levels leads to a loss of information. Fig.6.4 illustrates this feature using again the same waveform, but half the number of levels as compared to that of Fig.6.2. Thus, an optimum number of amplitude quantization levels is necessary.

6.2.3 Effect of smoothing

The waveforms shown in Figs. 6.1 to 6.4 are not the original responses but are the result of moving average filtering of the actual responses. This is because, the raw waveform contains many insignificant peaks. If such a raw data is given as input to the tree representation procedure, a number of irrelevant leaf nodes

result. Fig.6.5 illustrates this phenomenon for the same patient data used in Fig. 6.2. Hence, all the waveforms were smoothed before they were subject to the matching algorithm.

6.3 MATCHING

The ultimate aim behind this waveform matching was to compare each waveform with a standard reference waveform and to obtain a dissimilarity measure, which quantifies the amount of deformation of the waveshape. A waveform can always be modified by a number of successive operations like growing or shortening of a peak by one quantization level, deepening or shallowing of a valley by one quantization level and widening or narrowing of a peak or a valley by one sampling interval. It can be shown that these changes of a waveform shape directly correspond to node operations on its tree representation like father-son split or merge and brother-brother split or merge. Thus, by a suitable combination of the above mentioned node splitting and merging operations, any tree can be matched to another tree [Lu, 1984]. The number of tree operations to transform one tree to another is taken as the dissimilarity measure between the two corresponding waveforms.

6.3.1 Definition of terms

The terms used in the tree matching algorithm are explained here. **Postfix ordering** is the indexing of all the nodes of the tree by travelling through the leftmost subtree first, then the other subtrees and finally visiting the root [Horowitz and Sahni, 1985]. Travelling through each subtree is done similarly,

visiting its own first son nodes first and so on. A **region**, denoted R(a,b) is a collection of all the nodes of the tree that have postfix ordering between a and b. For this region, a and b are called the lower(LOW) and upper(UPP) limiting values. A set of regions, R_i, i = 1, ... , n is said to be **consistent** iff, n_s in R_i and n_t in R_{i+1} are such that n_t follows n_s in postfix ordering and n_s and n_t do not have a predecessor-descendent relation. A **minimum covering** of consistent regions R1, R2, ... , Rn is the smallest region that contains all the nodes in these n regions. For example, in Fig.6.1, regions R(1,2) and R(5,8) are consistent. Their minimum covering is region R(1,8).

6.3.2 Selection of brachial plexus response

Since there was no appreciable difference between the patients and normals with respect to the somatosensory cortical evoked potentials, the latter were not considered for tree based classification. In the case of the compound nerve action potentials from the digit and the elbow, there is a downward deflection in the main response which undershoots much below the base line of the waveforms. As already explained in section 6.2.1, the algorithm requires the entire waveform to be the interval for the first quantization level. In other words, the waveform must enclose the baseline at its time domain end points. Such a thing is difficult to achieve with the digit and elbow responses, except by gross modifications of the waveforms. Thus, they are also not suitable for tree representation using the above mentioned procedure. Hence, the Erb's point responses,

which have only upward deflections from the base line, were selected for analysis.

6.3.3 Tree matching algorithm

Let Tr be the reference normal tree or the template and let T be the tree to be matched with Tr. Matching is achieved by choosing regions on T to be possible matches for each subtree on Tr. The selected regions are ranked by their distance to the subtree and are then stored in a table known as a matching table created for the subtree.

Subtrees on T are processed in postfix sequence. To begin with, a current subtree is a terminal (leaf) node on Tr. Any region on T is considered as a possible match for this node. The distance between a terminal node and a region is simply the number of nodes in the region minus one. Then, the K regions with the smallest distances are entered in the matching table of the leaf node, where K is the predetermined size (number of entries) of any matching table. As an example, Table 6.1 shows the matching table for any terminal node on Tr, obtained from the tree given by Fig. 6.2. Entries in the first(LOW) and second(UPP) columns denote the limiting nodes of the matched region. The third column gives the error of the matched region. In the case of the entries numbered 1 to 12, the leaf node on Tr is matched to one of the leaf nodes on T. Seen in isolation from the rest of the tree, each of them is an optimal match and thus, the matching error is zero. Entry 13 gives the possibility of matching a null space. In this case, the error is 1. Entries 14 to 23 match the

leaf node to different regions on T, each having two nodes, one being a leaf node and the other, the father of the leaf node and having only one sun node. Thus, the matching error is again 1. Entries numbered 24 to 33 involve matched regions having 3 nodes each, one of which is a leaf node, resulting in an error of 2 and so on.

6.3.4 Matching of a node with one son

To match a node on Tr which has only one son, the matching table of son is taken. Suppose that an entry in the table is [s.low s.upp s.err]. Now, if the node on T with the index (s.upp+1) has only one son, then it is a simple situation. The corresponding entry for the node under consideration is [s.low s.upp+1 s.err]. If the node (s.upp+1) has ns(>1) number of sons, then the matched region for the father is still R(s.low,s.upp+1) but the matching error is s.err+ns-1. If (s.upp+1) indexed node is a leaf (no sons), then the corresponding entry is [s.low s.upp s.err+1].

6.3.5 Matching of a node with many sons

Assume that subtree under consideration on Tr consists of n smaller subtrees that are connected to a common node which is the root of current subtree. Suppose that the matching tables for all the n smaller subtrees have already been created. In such a case, a matched region on T for the subtree is the minimum covering of n consistent regions drawn from the n matching tables respectively. The coverings of the consistent combinations, ordered by their dissimilarity with reference to the current

subtree, go to make the matching table for the subtree. The first K possible matches with the least errors are taken and the rest are dropped. The distance between a covering and the current subtree is computed as the sum of the distance between a smaller subtree and its matched region for all the n smaller subtrees, plus the difference between the covering and the constituent n matched regions.

A situation may arise where none of the matched regions of a subtree is consistent with any of the set of matched regions of the other subtrees. In such a case, the matched region for that subtree is a null space. Then the required matched region for the root is obtained as the consistent combinations of matched regions of the remaining subtrees. The errors of each entry in the resultant table for the root is increased by the number of nodes in the unmatched subtree.

The matching algorithm thus involves a recursive procedure. When the recursion ends, the matching table for the root of Tr is obtained. The errors of each of the entries in this table are modified as follows. If Nm is the number of nodes in a matched region and Nt is the total number of nodes in T, then the error for that region is incremented by Nt-Nm. Now this table contains K different ways of matching Tr with T, starting from the smallest distance match to the Kth smallest distance match. The entry with the least error is the matched region on T for Tr. A node-to-node match between Tr and T can be obtained by backtracking the matching tables of nodes on Tr, beginning with

the root in a reverse order of the postfix ordering.

6.4 RESULTS AND DISCUSSION

Two reference trees were created : one (REF1.ERB) was the average of 21 responses from single trials of 21 normals ; the second (REF2.ERB) was the average of 42 waveforms including both trials of the 21 normals. The other normal data could not be included because of a difference in sampling rate. Tree representation and matching was performed with various values of time and amplitude quantization levels with each of the two reference trees individually. The optimum number of amplitude quantization levels is found to be 15 from the point of view of reasonable number of nodes without losing accuracy in representation of waveshape. Similarly, it is observed that a number of time quantization levels(XDIV) of less than 100 does not entail faithful representation of the peaks and valleys of the waveforms. Hence, matching was performed with 2 values of xdiv, namely, 100 and 300. Trials were undertaken to determine the number of times the moving average filter must be applied to the waveform for optimal performance of the matching algorithm. The results obtained for the optimum values of the parameters are tabulated in Table 6.2. Each trial (two/subject) of each subject (normal or patient) is separately matched individually with each of the two reference trees (REF1,REF2). The errors shown are the average of the matching errors of the two trials (recordings) for each subject.

The average error of the normal waveforms is 17.6 $\pm$ 5.6

using the optimal parameters (ydiv = 15 ; xdiv = 300 ; reference : ref2.erb ; number of smoothings = 15) and that of the patient waveforms is 26.8 $\pm$ 5.3. Thus, there is a highly significant ($p<.001$) separation between the values of distance of the normal and abnormal waveforms from the reference. The average error obtained while employing other values of the parameters are all listed in Table 6.3.

The (computation) time complexity of the tree matching algorithm is $O(NrK^2)$, where Nr is the number of tree nodes of the reference tree and K is the size of a matching table. It is found that for proper matching to be obtained, K must be greater than or equal to the number of nodes of T, say Nt. Thus, the complexity is $O(NrNt^2)$. The size of a skeletal tree is linear to the complexity of the corresponding waveform. Suppose that a waveform consists of np peaks ; then the upper bound of the size of its skeletal tree is nq * np, where nq is the number of quantization levels.

6.5 CONCLUSION

A waveform correlation scheme based on skeletal tree representation has been implemented to quantify the closeness in waveshape of brachial plexus response of any individual with the shape of the averaged normal waveform. This method has been found to be capable of handling a large degree of distortion between waveforms. The numbers of leaf and root nodes give an idea about the nature of the waveform and the algorithm is able to determine the abnormality of the waveshape.

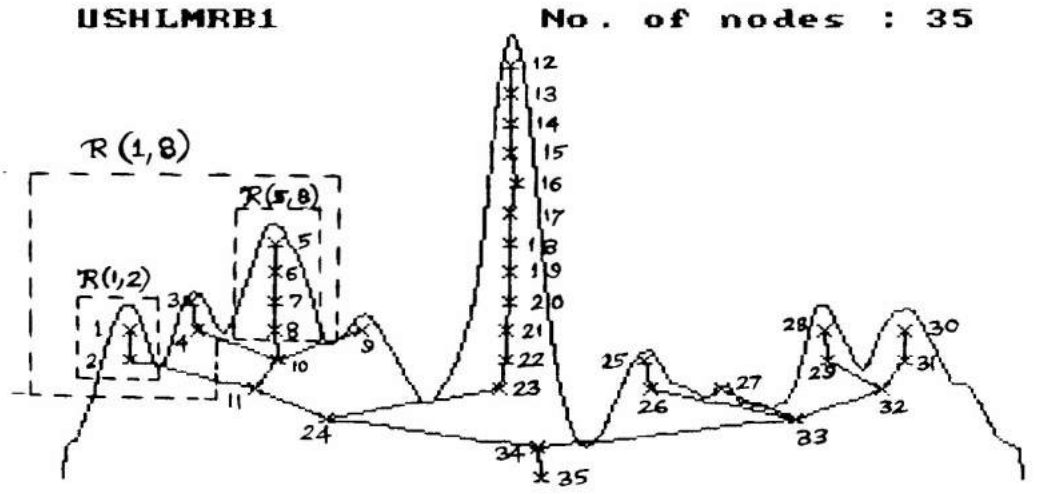


Fig.6.1. Skeletal tree of the Erb's potential from a normal

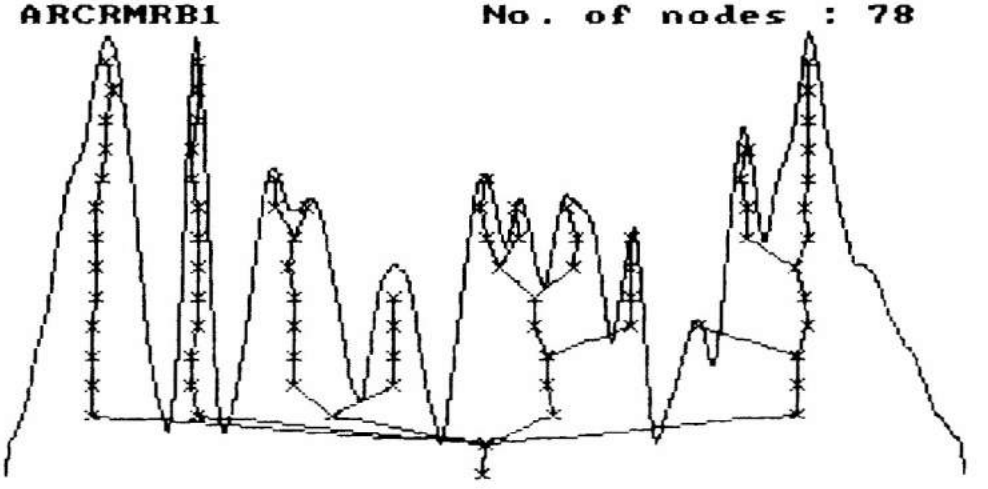


Fig.6.2. Skeletal tree of the Erb's potential from a patient

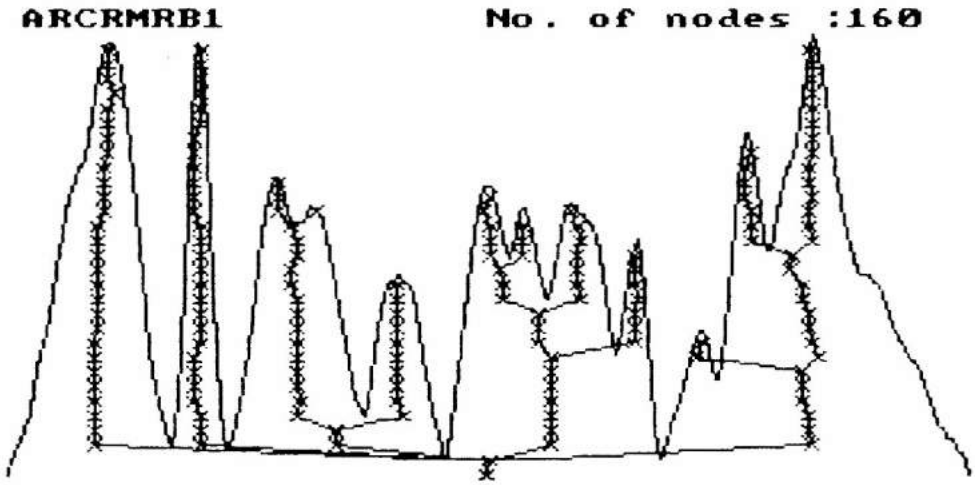


Fig.6.3. Illustration of the effect of too many quantization levels.
(waveform same as that of Fig.6.2)

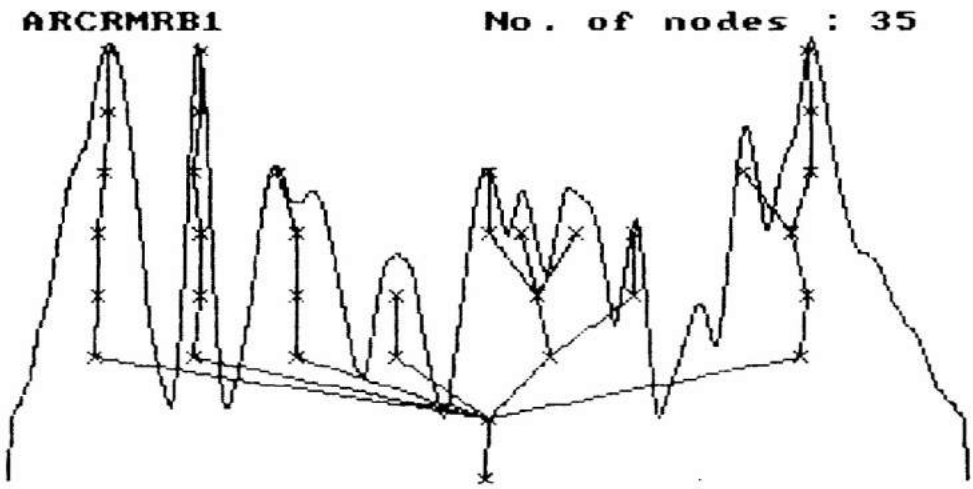


Fig.6.4. Illustration of the effect of inadequate quantization levels.
(waveform same as that of Fig.6.2)

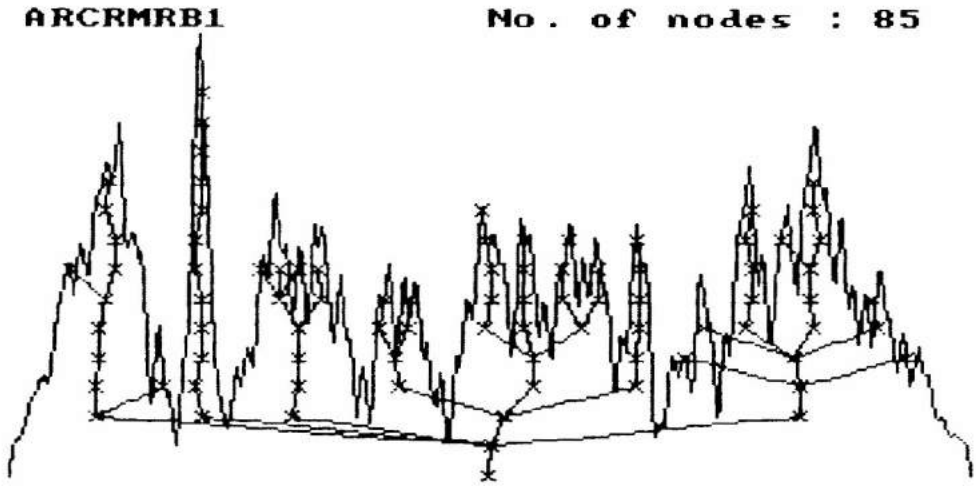


Fig.6.5. Illustration of the proliferation of irrelevant nodes resulting due to lack of smoothing.
(waveform same as that of Fig.6.2)

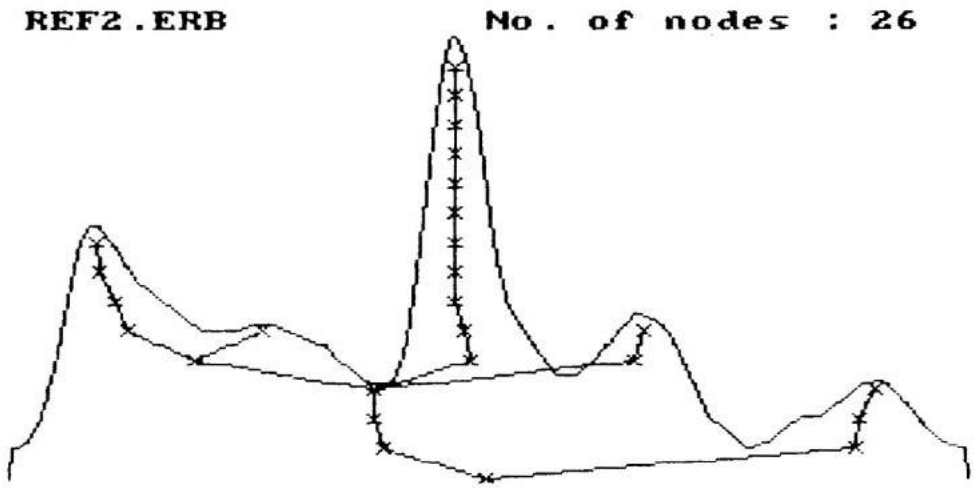


Fig.6.6. Skeletal tree of the reference waveform.

TABLE 6.1 MATCHING TABLE FOR A LEAF NODE ON Tr.
(The node indices pertain to the tree given by Fig. 6.2)

S.No.	LOW	UPP	ERR
1	1	1	0
2	14	14	0
3	27	27	0
4	29	29	0
5	36	36	0
6	41	41	0
7	44	44	0
8	47	47	0
9	52	52	0
10	59	59	0
11	60	60	0
12	64	64	0
13	0	0	1
14	1	2	1
15	14	15	1
16	27	28	1
17	36	37	1
18	41	42	1
19	44	45	1
20	47	48	1
21	52	53	1
22	60	61	1
23	64	65	1
24	1	3	2
25	14	16	2
26	36	38	2
27	41	43	2
28	47	49	2
29	52	54	2
30	60	62	2
33	64	66	2
32	1	4	3
33	14	17	3
34	27	30	3
35	36	39	3
36	52	55	3
37	60	63	3
38	64	67	3
39	1	5	4
40	14	18	4
41	27	31	4
42	64	68	4
43	1	6	5
44	14	19	5
45	27	32	5
46	41	46	5
47	64	69	5
48	1	7	6
49	14	20	6
50	27	33	6
51	64	70	6
52	1	8	7
53	14	21	7
54	27	34	7
55	1	9	8
56	14	22	8
57	27	35	8
58	1	10	9
59	14	23	9
60	41	50	9
61	1	11	10
62	14	24	10
63	41	51	10
64	1	12	11
65	14	25	11
66	60	71	11
67	1	13	12
68	14	26	12
69	60	72	12
70	27	40	13
71	60	73	13
72	41	56	15
73	59	74	15
74	41	57	16
75	59	75	16
76	41	58	17
77	59	76	17
78	1	77	76
79	1	78	77

TABLE 6.2 MATCHING ERRORS OF NORMAL AND PATIENT DATA
(for optimum values of parameters)

(xdiv : 300 ; ydiv : 15 ; smoothings : 15 ; ref : REF2.ERB)

SUBJ ID	ERROR	PAT. ID	ERROR	PAT. ID	ERROR
N 1	18.5	P 1R	28.5	P11L	35.5
N 2	12.0	P 1L	23.0	P12R	32.0
N 4	10.0	P 2R	28.5	P12L	21.0
N 5	29.0	P 2L	39.5	P13R	25.0
N 6	17.5	P 3R	20.0	P13L	32.0
N 7	18.5	P 3L	15.5	P14R	28.5
N 8	17.0	P 4R	29.5	P14L	27.0
N 9	24.5	P 4L	28.5	P15R	28.0
N13	20.0	P 5R	22.5	P15L	29.0
N14	23.5	P 5L	20.5	P16R	22.0
N15	17.0	P 6R	22.5	P16L	19.5
N16	13.5	P 6L	35.0	P17R	31.5
N17	15.5	P 7R	25.5	P17L	21.0
N18	12.5	P 7L	26.0	P18R	31.5
N19	15.0	P 8R	38.5	P18L	22.5
N20	20.0	P 8L	20.0	P19R	29.0
N21	18.0	P 9R	31.5	P19L	33.0
N22	9.0	P 9L	27.0	P20R	22.0
N23	22.0	P10R	26.0	P20L	30.0
N24	9.0	P10L	28.0	P21R	19.0
N25	28.5	P11R	23.5	P21L	29.5

TABLE 6.3 MEAN ERRORS FOR NORMALS AND PATIENTS USING DIFFERENT VALUES OF PARAMETERS
(ydiv = 15 for all cases)

PARAMETERS	MEAN ERROR FOR NORMALS	MEAN ERROR FOR PATIENTS
REF : REF2.ERB		
SMTH^ = 15		
XDIV~ = 100	17.3 + 5.8	25.4 + 4.6
XDIV = 300	17.6 + 5.6	26.8 + 5.3
SMTH = 25		
XDIV = 100	16.4 + 4.4	22.0 + 3.4
XDIV = 300	16.6 + 4.6	22.3 + 3.4
REF : REF1.ERB		
SMTH = 15		
XDIV = 100	18.2 + 6.0	26.6 + 4.8
XDIV = 300	19.0 + 6.2	27.6 + 5.5
SMTH = 25		
XDIV = 100	17.3 + 5.0	22.8 + 3.9
XDIV = 300	17.6 + 5.2	23.2 + 4.3

^ SMTH : no. of times the waveforms is smoothed before being subjected to the matching algorithm.

~ XDIV : the no. of time (x-axis) quantization levels.

7. CONCLUSION

7.1 OVERVIEW OF THE WORK

The present study was conceived in order to evaluate quantitatively, the relevance of electrophysiological techniques in the early diagnosis of leprosy. The work involved application of various procedures for the analysis of the peripheral and central conduction data obtained from a number of subjects.

Every leprosy patient suffers from peripheral nerve involvement as a result of the disease. This may vary from the involvement of intradermal nerves in a cutaneous patch to a major lesion in the nerve trunk. Thus, there is no nonneural leprosy. Despite the magnitude of the problem of leprosy incidence in the world today and the fact that about 20 percent of the patients suffer from major sensory and motor neurological deficits, extensive electrophysiological studies in leprosy have been few. Further, relatively more work has been done on motor conduction than on sensory conduction.

Since sensory loss precedes motor deficit in almost all the patients, with the idea of early detection in mind, only sensory conduction studies have been performed in this study. A 'neuroaverager card' has been designed, developed, tested and then incorporated in the commercially available microcomputer system in India, thus making a totally indigenous medical equipment, which is not, till today, manufactured in India. This system is capable of obtaining brainstem auditory, visual and somatosensory evoked potentials and electromyogram besides nerve

conduction data. Thus, monitoring of both peripheral and central nervous systems is possible. The system has complete software support for smoothing, cursor measurements and further processing of the acquired responses. Thus, the system developed here has all the features available in most commercial EP monitoring systems, with the advantage of a single board to fit into any IBM PC-XT compatible. This system has been used to obtain data from 67 median nerves, 25 coming from one of the upper limbs of 25 healthy youth as controls and the rest from both sides of 21 Hanseniasis patients.

By stimulating the median nerve at the wrist, sensory nerve action potentials were recorded from 3 peripheral locations and event related potentials were recorded from the contralateral somatosensory cortex. The stimulus threshold, amplitudes and durations of the responses, conduction velocities of the nerve segments involved and the central conduction time were all obtained from the recorded waveforms. These data were correlated with the clinical data of the patients. The principal time domain variables that demarcate the healthy responses from the pathological ones were extracted by subjecting the data to discriminant analysis. The distinction between the normal and abnormal potentials in their behaviour in the frequency domain has also been studied. Finally, the brachial plexus' waveforms were represented by a skeletal tree structure and the deviation of their shapes from that of an average normal waveform was quantified.

7.2 SUMMARY OF THE RESULTS

The mean central conduction time of patients is the same as that of healthy controls of matched age. The mean amplitude of the cortical potentials is also nearly equal to that of normals. Further, the average frequency spectra of somatosensory evoked potentials of normals and patients are indistinguishably identical. The discriminant analysis too has clearly shown that none of the characteristics of the SEPs are capable of discriminating between normal and abnormal populations.

The waveshapes of all the three peripheral potentials in the case of patients appreciably differ from those of controls. The distortion in the waveforms of Erb's point responses from patients, as quantified by the tree-based matching procedure, is considerably higher than the error in normal responses with reference to an average normal Erb's potential. The second iteration of discriminant analysis showed that the discriminating power of the NCV in the arm segment as well as the amplitude of the Erb's potential are poor compared to the those of the distal potentials.

The sensory and motor thresholds of stimulation have been found to be considerably raised in patients. There is no significant difference between normals and patients with respect to the mean values of the interpeak latencies. There is an appreciable reduction in the mean value of the sensory NCVs of the two distal segments(forearm and palm) though correlation with the clinical symptoms could not always be established. The

amplitudes of the two distal potentials (digital and elbow) have significantly decreased with near total correlation with clinical findings such as sensory and motor damage. This reduction in amplitudes is in spite of the higher stimulus strengths employed because of the increased thresholds of patients. The discriminant analysis gave a linear function involving only 3 parameters as an effective classifier, capable of distinguishing between normal and abnormal median nerve responses. These predictor variables are the stimulus strength S, the NCV of palm V_p and the amplitude of the digit response A_d.

The patient response waveforms have a number of small peaks spread out in time indicating different arrival times in different nerve fibres demyelinated or otherwise damaged to different degrees.

7.3 CONCLUSIONS

Electrophysiological studies are useful tools for evaluating the nature and severity of nerve damage in leprosy. The amplitudes of the distal peripheral potentials are much better indicators of leprous neuropathy than the sensory NCVs. This significant correlation of amplitudes with clinical features has not been conclusively studied or reported by anybody so far. Most of the earlier researchers have tried to relate EMG, motor NCV and rarely sensory NCV with the clinical dysfunction. Thus an extremely useful fact has been missed by all of them. The study of distal conduction in the upper limbs may well be used to screen a population of suspected infection by M.leprae. Early

analysis of ulnar nerve CNAPs is recommended for this purpose. It appears that the electrodiagnostic application of NCVs in leprous neuritis should be limited to the relatively advanced cases. The amplitudes, conduction times and frequency spectra of cortical potentials all go to confirm the fact of non-involvement of central nervous system in Hansen's disease.

Functional derangement of nerves is revealed by nerve conduction studies before the appearance of clinical signs. The reduction in amplitude of responses in such cases may be an early sign of median nerve involvement, thus being of some prognostic value. With this finding, therapy can be directed to the nerve earlier enough to prevent possible development of any disability. Serial evaluations of sensory conduction could aid in early detection as well as in monitoring both the progress of the disease and the effect of the treatment. It could also be used to help evaluate and compare the various methods of treatment.

It is significant that impairment of the NCV was not always found even with patients having symptoms of neural involvement. This should be compared with the observations in other chronic polyneuropathies eg., peroneal muscular atrophy and related syndromes where impairment of motor conduction in the long peripheral nerves is marked in symptomatic cases, and even some mildly affected or asymptomatic cases of Charcot-Marie-Tooth disease [Dyck et al., 1963 ; Yudell et al., 1965]. This observation could possibly be used in differential diagnosis of leprous neuropathy, based on further conclusive studies.

7.4 DESIGN OF A PORTABLE FIELD UNIT

Early diagnosis of the disease is a vital component of leprosy control in India. Based on the work summarised above, electrophysiologically there seems to be a good possibility of diagnosing early cases of the disease. A stand-alone, portable neuroaverager unit has been designed based on Zilog Z80A microprocessor and is under development. This system has been specifically designed to be a field unit, which can be conveniently carried and used by field survey health care staff to identify early cases of leprosy. It has got a single channel, programmable instrumentation amplifier and only an electric stimulator, isolated and intensity as well as duration programmable.

7.5 FUTURE WORK

Though measurement of central conduction time from the latency of the Erb's point potential has been adopted by earlier workers [Chiappa et al., 1980] while studying other neurological disorders, it will be ideal to calculate it using the latency of the response recorded from the C2 vertebral spine as reference. To obtain this potential, electrodes are placed at the posterior midline of the neck at the second cervical vertebra (usually about 4 cm below the inion). However, since the neural tissue is a little deeper here and from the point of view of the location of the site too, it is better to use needle electrodes for recording from C2. Since only surface electrodes were employed in this study because of other practical considerations, consistently good C2 responses could not be obtained by the

author and hence the data collected was not presented in this thesis. However, it will be worthwhile to include C2 also as one of the recording sites in future studies.

Electromyography and motor conduction studies, if included, will make this study a more complete one. They could not be performed in the reported work here because it would have increased the recording time for a patient too much to be practicable. However, recording with a 4 or more channel machine will reduce the total testing time as well as patient discomfort, since, with one set of stimuli, all the sensory and motor responses could be picked up.

It is important to note that the temporally dispersed peaks observed in the time domain plots of Figs. 3.6 to 3.9 (panel b) from the patients are consistently present in spite of the fact that most of the waveforms recorded are averages of 16, 64 or 128 responses. An analysis which will study the energy density with respect to time could reveal more information in this regard. Perhaps, these peaks constitute a modulating frequency, probably at 1.5 KHz, seen as a peak in the frequency spectra. To what extent a reduced amplitude is due to increased temporal dispersion or to block of fibres or loss of fibres, is not known. A comprehensive modelling of the conduction mechanism in the nerve should be developed incorporating the changes produced by the degradation of myelin. The model must explain the increased motor threshold of stimulation, temporal dispersion of peaks, the reduction in amplitudes and also reveal the sources of the

specific frequency peaks observed in the spectra.

A protocol could be drawn up to assess the response of the nerves to varied therapeutic regimens.

Ideally a comprehensive study must be undertaken by a team, consisting of engineers, physicians, surgeons, pathologists and also mathematicians. EMG, sensory and motor conduction tests must be carried out on the affected muscles/nerves and the results correlated with the clinical observations. Wherever cases are referred to for surgery for nerve decompression or correction of deformities, the above mentioned studies can be supplemented by histopathologic studies.

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ABBREVIATIONS & NOTATIONS

ADC : Analog to digital converter

A_b : Peak to peak amplitude at Erb's point, P11 - N9

A_d : Peak to peak amplitude at third digit, P4 - N3

A_e : Peak to peak amplitude of CNAP at elbow, P6 - N5

A_s : Peak to peak amplitude of SEP, P22 - N19

BAEP : Brainstem auditory evoked potential

CCT : Central conduction time

CNAP : Compound nerve action potential

CNS : Central nervous system

CT : Computed tomography

DG : Digit

EEG : Electroencephalography

EMG : Electromyography

EP : Evoked potential

ERP : Event related potential

ILC : Internal Longitudinal Current

LB : Elbow

L_d : Length of nerve between site of stimulus and digit

L_e : Length of nerve between site of stimulus and elbow

L_{ep} : Length of nerve between elbow and Erb's point

LL : Lepromatous leprosy

LM : Left median nerve

MNCV : Motor nerve conduction velocity

NCT : Nerve conduction time

NCV : Nerve conduction velocity

Nx : Negative peak occuring around 'x' msec.

Px	:	Positive peak occuring around 'x' msec.
RB	:	Erb's point
RM	:	Right median nerve
S	:	Stimulus
SC	:	Scalp
SEP	:	Somatosensory evoked potential
SNCV	:	Sensory nerve conduction velocity
TT	:	Polar tuberculoid leprosy
V_a	:	NCV of arm segment
VEP	:	Visual evoked potential
V_{fa}	:	NCV of forearm segment
V_p	:	NCV of palm segment